Biological Therapies

16

16.1 General Background

Bipolar disorder is complex, with different facets and stages, and it is not exactly known how this affects the everyday clinical practice. Its treatment is also complex, and unfortunately the hard data are insufficient to support all decisions. Reports at the case report level do exist, but they should not be considered sufficient (Fountoulakis et al. 2004b, 2007a). Rigorously collected data are available only for a limited number of agents and for selected aspects of the disease (Fountoulakis 2008, 2010b, 2012a; Fountoulakis et al. 2004a, 2005, 2007b, 2008a, 2012b; Nivoli et al. 2011). There are a number of issues which are still open to discussion. These include the definition of maintenance and of refractoriness (Fountoulakis 2012b) but mainly what is the most appropriate sequence of steps in the long-term treatment (Fountoulakis and Vieta 2008). The current chapter will systematically review the hard pharmaceutical data on the treatment of BD. As it will focus on efficacy data specifically for BD, only a brief description of the most important agents or groups of agents and their adverse events will be made, since these can be found easily in other books and sources.

16.1.1 Lithium

Lithium is a rather rare chemical element with atomic number 3 and its symbol is 'Li'. It belongs to the alkali metal group, and it is the lightest metal and the least dense solid element. Two stable lithium isotopes can be found in nature. It is soft, silver white and highly reactive and inflammable. Because of this, in nature it always occurs in pegmatitic minerals, is present in ocean water and usually and is obtained from brines and clays.

It was discovered in 1800 by the Brazilian chemist and statesman José Bonifácio de Andrada e Silva (1763–1838) in a mine on the island of Utö, Sweden, in the form of petalite ($LiAlSi_4O_{10}$). After extensive research on petalite, in 1817 Johan August

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Arfwedson (1792–1841) identified a new element which the head of the laboratory Jöns Jakob Berzelius (1779–1848) gave the name 'lithion' or 'lithina', from the Greek word 'lithos' (stone) and from the Greek word λιθος (transliterated as lithos, meaning 'stone'). The pure element was isolated in 1821 by William Thomas Brande (1788–1866) by electrolysis of lithium oxide. The method of electrolysis made large quantities of lithium available, and the commercial production and usage begun in the late nineteenth century. Lithium has several important applications in industry, ranging from glass and ceramics to lithium batteries and high-tech weapons. Today most lithium is used in batteries.

Although trace amounts exist in all organisms, there are no known physiological functions for lithium, and live organisms can survive without it. In spite of this, lithium has been used as medication already since the late nineteenth century.

In 1847 Alfred Baring Garrod (1819–1907) announced that he had discovered uric acid in the blood of gouty patients. Since at least in the laboratory, lithium could dissolve uric acid crystals isolated from the kidneys, and using lithium to dissolve urate in the body seemed a logical step. Garrod discovered that gouty uric acid deposits in finger joints are soluble in vitro in a lithium solution, and Alexander Ure (early nineteenth century–1866) in 1843 introduced lithium into medicine by showing that in vitro a uric acid bladder stone lost weight in a lithium carbonate solution. It is interesting that according to the works of Armand Trousseau (1801–1867) in France and Alexander Haig in the UK, mania and depression are related to the uric acid nosology (brain gout). Although Garrod made lithium treatment of gout widely known in 1859, unfortunately it was proven that the levels of lithium needed to dissolve urate in the body were toxic (Marmol 2008; Shorter 2009; Johnson and Amdisen 1983; Strobusch and Jefferson 1980). Following these observations and suggestions, a number of beverages included lithium as their component in the late nineteenth and early twentieth century (Fig. 16.1). Charles Leiper Grigg (1868–1940) introduced a lemon-lime soft drink in 1929 under the label 'Bib-Label Lithiated Lemon-Lime Soda' which soon changed to 7 Up (Fig. 16.2). However by 1948 lithium has been removed from

Fig. 16.1 Example of beverages which included lithium as their component in the late nineteenth and early twentieth century

Fig. 16.2 The original 7 Up-included lithium

all beverages because of cases of toxicity, and its free marketing was prohibited (Marmol 2008). In parallel, a number of remedies with lithium were marketed in the early twentieth century (Figs. 16.3 and 16.4) and were mostly indicated for the control of renal calculi and 'uric acid diathesis' (Shorter 2009).

The first psychiatric indication for lithium came from Silas Weir Mitchell (1829–1914), a neurologist from Philadelphia, in 1870. Mitchell recommended lithium as an anticonvulsant and hypnotic (Mitchell 1870) and letter for 'general nervousness' (Mitchell 1877). Already in 1871, William Alexander Hammond (1828–1900) was maybe the first to prescribe a modern and effective psychotropic agent, and this was lithium (Mitchell and Hadzi-Pavlovic 2000). At that time, he was the professor of Diseases of the Mind and Nervous System at the Bellevue Hospital Medical College in New York. The Danish psychiatrist Carl Lange (1834–1900) used lithium in the treatment of recurrent brief depression in 1886, while his brother, Frederik Lange (1842–1907), used lithium in the treatment of 35 melancholic depressive patients (including some milder forms of BD) in 1894 (Lenox and Watson 1994).

However in spite of encouraging results, by the turn of the twentieth century, the 'brain gout' theory of mood disorders disappeared as a medical entity, and the use of lithium in psychiatry was abandoned.

After the WWII, in 1949 in the Bundoora Repatriation Hospital, a veterans hospital in a suburb of Melbourne, the Australian John Cade (1912–1980) injected urine from patients with schizophrenia to guinea pigs to test the hypothesis that mania is caused by intoxication by a normal body element circulating in excess, while melancholia is the corresponding deprative condition. He used lithium urate as control and observed it caused the rodents to be tranquilized. In fact it is possible that the animals were lethargic because of lithium toxicity, and this seems to be the case with the patients of William Alexander Hammond, since the dosages reported by both researchers lead to lithium intoxication. In 1949 Cade reported positive

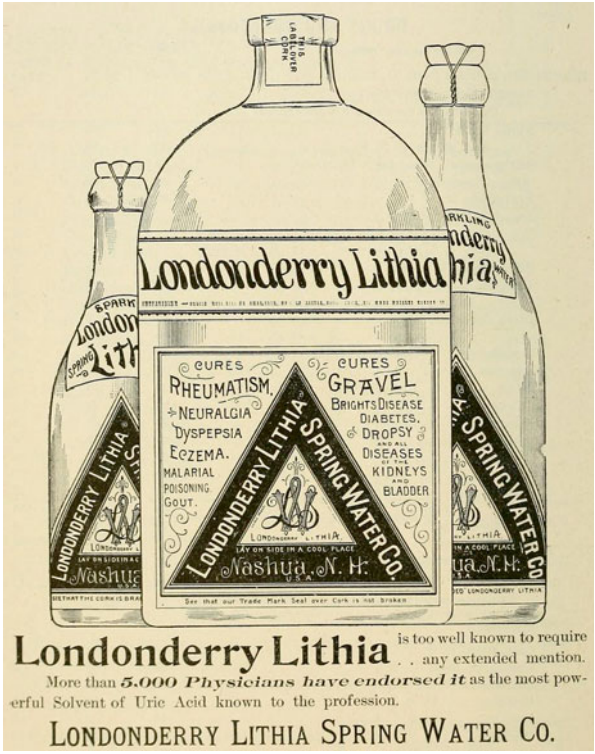

Fig. 16.3 Example of remedies with lithium which were marketed in the early twentieth century and were mostly indicated for the control of renal calculi and 'uric acid diathesis'

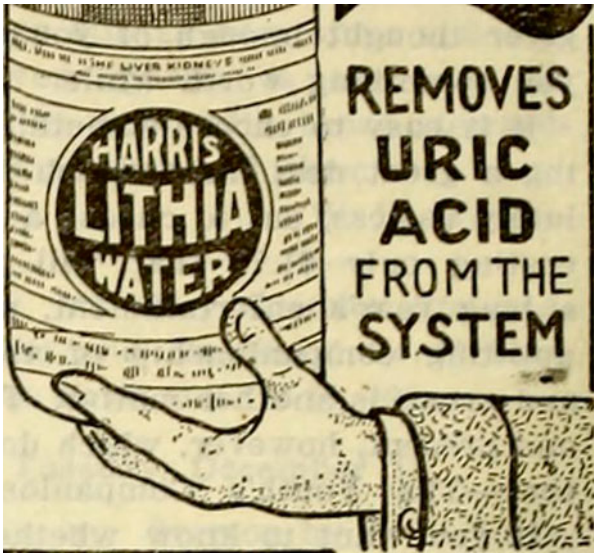

Fig. 16.4 Example of remedies with lithium which were marketed in the early twentieth century and were mostly indicated for the control of renal calculi and 'uric acid diathesis'

results from the treatment of ten acutely manic patients (Cade 1949, 2000); however, 2 years later he reported the first death because of lithium toxicity in a patient whose bipolar illness otherwise responded extremely well to treatment. Subsequent research with other ions (rubidium, cesium, lanthanum, neodymium and strontium) gave no positive results.

During the 1950s several researchers studied lithium and its usefulness in BD (Noack and Trautner 1951). However the important contribution that made the difference came from Denmark again in 1952, when Erik Stromgren (1909–1993), head of the Aarhus University psychiatric clinic in Risskov at that time, asked Mogens Schou (1918–2005) to undertake a randomized controlled trial of lithium in mania (Bech 2006). Mogens Schou was not a psychiatrist but a physician specialized in clinical chemistry and had observed a dramatic therapeutic effect of long-term lithium treatment in his younger brother. Schou randomized acutely manic patients with a flip of a coin to lithium or placebo, and in 1954 he published the results which made a significant impact (Schou et al. 1954). However lithium was still difficult to administer and blood levels a matter of guesswork. The situation changed with the introduction of the Coleman flame photometer in 1958 which made to monitor plasma lithium levels much more precisely in comparison to the previously used Beckman photometer.

It was, however, the Danish psychiatrist Poul Christian Baastrup (1918–2002) who demonstrated in 1964 the efficacy of lithium for the maintenance phase (Baastrup 1964). In the USA in 1960 Samuel Gershon joined the Schizophrenia and Psycho-pharmacology Joint Research Project of the University of Michigan at the mental hospital in Ypsilanti, Michigan, and the same year along with Arthur Yuwiler, also at Ypsilanti, they published the first North American paper on lithium (Gershon and Yuwiler 1960). For the next few years, there was significant academic opposition to the use of lithium as the standard treatment for BD, and much emphasis was given to its toxicity. Aubrey Lewis (1900–1975), professor of psychiatry and head of the Maudsley, considered lithium treatment 'dangerous nonsense', and Michael Shepherd (1923–1995) was also extremely negative towards it and suggested that lithium was toxic in mania and that claims of efficacy for it in preventing depression rested on 'dubious scientific methodology' (Blackwell and Shepherd 1968; Shepherd 1970; Blackwell 1969, 1970, 1971, 1972). However later studies established lithium and robustly linked it to the treatment of all phases of (Schou et al. 1970; Angst et al. 1969, 1970; Baastrup et al. 1970; Baastrup and Schou 1967; Bech 2006; Schioldann 1999, 2006, 2011; Johnstone et al. 1988; Mitchell and Hadzi-Pavlovic 2000). Later Fred Goodwin suggested that it could be also useful in the treatment of depression as add-on to antidepressants (Goodwin et al. 1969a, b, 1972, 2003; Goodwin 2002; Goodwin and Zis 1979). The recommended serum lithium levels were determined with certainty in 1976 (Bech et al. 1976). The term 'mood normalizer' was proposed by Mogens Schou for lithium (Schou 1963) after the term 'mood stabilizer, which was used during the 1950s to refer to a combination of amphetamine and a barbiturate to treat patients with neurotic instability but not patients with BD.

Lithium treatment for BD was approved in 1961 in France, in 1966 in the UK, in 1967 in Germany and in 1970 in Italy and the USA. In 1974, this application was

extended to its use as a preventive agent for manic–depressive illness (Mitchell and Hadzi-Pavlovic 2000).

The specific biochemical mechanism of lithium action in mania is unknown. Interestingly unlike many other psychoactive drugs, it does not have any psychotropic effect in normal individuals at therapeutic concentrations. Treatment with lithium demands regular serum level tests and monitoring of thyroid and kidney function. Dehydration can result in increasing lithium levels. Serum lithium concentrations are recommended to be in the 0.4–1.2 mmol/l range (lower end of the range for maintenance therapy and the elderly, higher end for children) on samples taken 12 h after the preceding dose (Amdisen 1977; Chen et al. 2004; Solomon et al. 1996; Perlis et al. 2002).

The adverse effects of lithium include leukocytosis, polyuria and polydipsia, dry mouth, hand tremor, headache, neurocognitive problems, confusion, muscle weakness, ECG changes, nausea, vomiting, diarrhoea or constipation, muscle twitch, vertigo, EPS, euthyroid goitre, hypothyroidism, acne, hair loss and hair thinning, renal toxicity and renal interstitial fibrosis, seizures, coma, hallucinations, erythema multiforme, Brugada syndrome, sinus node dysfunction, pseudotumor cerebri, increased intracranial pressure and papilloedema and weight gain or loss. Lithium is also a teratogen, causing birth defects in a small number of newborn babies, including Ebstein's anomaly (Shepard et al. 2002). Most adverse effects are dose dependent. Dehydration in people taking lithium salts can be very hazardous, especially when combined with lithium-induced nephrogenic diabetes insipidus with polyuria. Lithium inhibits the action of the antidiuretic hormone causing an inability to concentrate urine, which leads to consequent loss of body water and thirst. Patients and therapists should be alert on heat and diarrhoea and other causes of dehydration. On the other hand, another danger is that rapid hydration may cause hyponatraemia with its danger of toxic sodium concentrations in plasma.

Lithium concentrations can be increased with concurrent use of diuretics especially loop diuretics and thiazides as well as with nonsteroidal anti-inflammatory drugs. Co-administration with antidepressants increases the risk of serotonin syndrome, and with antipsychotics it increases the risk for neuroleptic malignant syndrome.

Lithium toxicity manifestations include nausea, vomiting, diarrhoea, asthenia, ataxia, confusion, lethargy, polyuria, seizures and coma, coarse tremor, muscle twitching, convulsions and renal failure. Several authors have described a 'Syndrome of Irreversible Lithium-Effected Neurotoxicity' (SILENT), associated with episodes of acute lithium toxicity or long-term treatment within the appropriate dosage range. Symptoms are said to include cerebellar dysfunction (Ikeda et al. 2010; Porto et al. 2009; Adityanjee et al. 2005; Adityanjee 1989, 1987). Unfortunately, in long-term use, toxic effects might be induced even at therapeutic plasma levels (Fountoulakis et al. 2008c).

16.1.2 Antiepileptics

Although in much of the literature, the terms 'anticonvulsants' or 'antiepileptics' are used interchangeably with the term 'mood stabilizers', and only three antiepileptics (valproate, carbamazepine and lamotrigine) have proven efficacy in BD.

16.1.2.1 Valproate

Sodium valproate is the sodium salt of valproic acid. It is an anticonvulsant efficacious in the treatment of epilepsy (all partial and generalized seizures including absence seizures) as well as in the prevention of migraine headaches. It was first synthesized in 1882 by B.S. Burton as an analogue of valeric acid which can be found naturally in valerian and was used in the cosmetics industry. Valeric acid appears similar in structure to GABA but lacks the alcohol and amine functional groups that contribute to the biological activities of the GABA. Valproic acid was used for long in laboratories as a 'metabolically inert' solvent for organic compounds, and until in 1962 Pierre Eymard accidentally discovered its anticonvulsant properties while using it as a vehicle for other compounds that were being studied for antiepileptic properties (Meunier et al. 1963). Valproic acid was approved as an antiepileptic for the first time in 1967 in France.

Its mechanism of action includes weak blocking of sodium ion channels and weak inhibition of enzymes that deactivate GABA (e.g. GABA transaminase). It is unclear whether it also stimulates GABA synthesis.

Adverse effects include tiredness, tremor, nausea, vomiting, sedation and gastrointestinal symptoms as well as reversible hair loss in about 10 % of patients. Also some patients experience vision problems, endocrinological disorder (increased testosterone production in females and menstrual irregularities), memory problems, weight gain, infections, drowsiness and headache, liver damage, polycystic ovaries, movement disorders (even hallucinations, anxiety and confusion), swollen pancreas, low body temperature and potentially life-threatening blood abnormalities (e.g. low platelet count). Valproate has the highest risk of birth defects of any of the commonly used antiepileptic drugs during pregnancy (Cummings et al. 2011). Overdose results in tremor, respiratory depression, coma and metabolic acidosis and eventually can result to death. Serum or plasma levels of valproic acid concentrations should be in the range of 50–150 mg/l for the treatment of BD.

16.1.2.2 Carbamazepine

Carbamazepine is an antiepileptic efficacious against partial seizures, generalized tonic–clonic seizures and mixed seizures and also useful for the treatment of trigeminal neuralgia. It was discovered by chemist Walter Schindler at J.R. Geigy AG (today Novartis) in Basel, Switzerland, in 1953. It was first marketed as a drug to treat trigeminal neuralgia in 1962 and as an antiepileptic in the UK since 1965 and the USA since 1974. In 1971 the first studies concerning BD appeared in Japan (Okuma and Kishimoto 1998).

The mechanism of action of carbamazepine includes the stabilization of the inactivated state of sodium channels, making thus reducing the excitability of the neurons. It has also been shown to bind to GABA receptors (Granger et al. 1995).

The most common adverse effects with carbamazepine treatment may include drowsiness, dizziness, headaches and migraines, motor coordination impairment, nausea, vomiting, constipation, cardiac arrhythmias, blurry or double vision, aplastic anaemia or agranulocytosis and a dangerous or even fatal skin reaction (Stevens–Johnson syndrome and toxic epidermal necrolysis). It can also exacerbate

pre-existing hypothyroidism. It can cause syndrome of inappropriate antidiuretic hormone, and it can aggravate juvenile myoclonic epilepsy and other types of epilepsy, especially absence seizures (Liu et al. 2006).

Among the agents used in the treatment of BD, carbamazepine is the drug most potent to interactions with other medication. It is a CYP450 inducer, and thus it might increase the metabolism and elimination of many agents, including warfarin, lamotrigine, phenytoin, theophylline, valproic acid, benzodiazepines and some antipsychotics. It also reduces the effectiveness of birth control pills thus leading to unexpected pregnancies. Other agents, like erythromycin, cimetidine, valproic acid, valnoctamide and calcium channel blockers as well as grapefruit juice, decrease carbamazepine metabolism and increase its serum availability often to toxic levels. As a drug that induces cytochrome P450 enzymes, it accelerates elimination of many benzodiazepines and decreases their action.

Carbamazepine is teratogenic and is associated among others with the development of spina bifida (Jentink et al. 2010), neurodevelopmental problems and delays (Cummings et al. 2011) craniofacial defects, cardiovascular malformations and hypospadias.

16.1.2.3 Lamotrigine

Lamotrigine is an antiepileptic efficacious in the treatment of focal seizures, primary and secondary tonic–clonic seizures and seizures associated with Lennox–Gastaut syndrome. It was marketed for the first time in 1994. It is chemically different to other antiepileptics.

Lamotrigine is a triazine derivate that inhibits voltage-sensitive sodium channels, leading to stabilization of neuronal membranes. It also blocks calcium channels and has a weak 5-HT3 receptor inhibition. Probably other actions also exist since lamotrigine exerts a variety of effects and adverse events which cannot be explained by its above pharmacodynamics properties alone (Rogawski and Loscher 2004a, b; Lees and Leach 1993). It is metabolized by hepatic glucuronidation.

Its adverse effects include life-threatening skin reactions, including Stevens–Johnson syndrome, DRESS syndrome and toxic epidermal necrolysis. Since December 2010, lamotrigine carries an FDA black box warning for aseptic meningitis. Other adverse events include loss of balance or coordination, double vision, blurred vision, dizziness, drowsiness, insomnia, anxiety, vivid dreams or nightmares, dry mouth, mouth ulcers, memory and cognitive problems, runny nose, cough, indigestion, abdominal pain, weight loss, missed or painful menstrual periods, vaginitis and leukopaenia.

Certain contraceptives decrease serum levels of lamotrigine (Reimers et al. 2005).

Lamotrigine has low teratogenic action; however, if used during the first trimester, it may increase the risk for cleft lip and palate malformation in newborns.

Lamotrigine has fewer drug interactions than other antiepileptics; however, caution is needed when co-administered with hepatic enzyme-inducing medications (Anderson 1998).

16.1.3 Antipsychotics

Antipsychotics or neuroleptics (also called previously major tranquilizers) were developed initially for the treatment of schizophrenia and psychotic symptoms.

Chlorpromazine was the first to be discovered in 1952 and initially was developed as an anaesthetic agent for general surgical use. The French Henri Laborit (1914–1995) reported that chlorpromazine was inducing indifference towards traumatic events in otherwise mentally healthy persons. Jean Delay (1907–1987) and Pierre Deniker (1917–1998) were the first to use it as monotherapy in agitated psychosis.

Antipsychotics are grouped into the first-generation antipsychotics (FGAs), also called typical antipsychotics, and the second-generation agents (SGAs), also called atypical antipsychotics. The common pharmacodynamics property of all antipsychotic agents is dopamine D2 receptor blockade. Most antipsychotics also affect a number of other neurotransmitters.

The most frequent adverse events for FGAs are extrapyramidal symptoms (EPS) and hyperprolactinaemia, while weight gain and metabolic abnormalities are caused mainly by SGAs. Other adverse effects include sedation, headaches, dizziness, diarrhoea, sexual dysfunction, osteoporosis, orthostatic hypotension, anticholinergic side effects, memory problems, angle-closure glaucoma, blurred vision, constipation, dry mouth or hypersalivation, agranulocytosis, leukopaenia, and neutropaenia and QT prolongation. Tardive dyskinesia and neuroleptic malignant syndrome are the most severe adverse events.

16.1.4 Antidepressants

Antidepressants are agents used for the treatment of depression but also of anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and other neurological and psychiatric conditions.

In 1951, research on the two new anti-tuberculosis agents isoniazid and iproniazid developed by Hoffman–LaRoche, by Irving Selikoff (1915–1992) and Edward Robitzek (1912–1984) at Sea View Hospital on Staten Island suggested that the two agents also possessed some psychotropic properties (Selikoff and Robitzek 1952; Robitzek et al. 1952; Selifoff et al. 1952). Following these reports, in 1952 the Cincinnati psychiatrist Max Lurie (born 1920) treated some of his patients with these agents and together with Harry Salzer (born 1906) they reported that isoniazid improved depression in two-thirds of their patients. They also introduced the term antidepressant (Salzer and Lurie 1953). A year before, in France, Jean Delay with the resident Jean-Francois Buisson reported the positive effect of isoniazid on depressed patients, but they published these results years later (Delay and Buisson 1958). Roche has also produced iproniazid which showed a greater psychostimulant effect, but also more pronounced toxicity (Robitzek et al. 1953). Nathan Kline supported its use as an antidepressant, but eventually in 1961 it was withdrawn from the market because of lethal hepatotoxicity (Lopez-Munoz et al. 2007).

In 1957 the Swiss psychiatrist Roland Kuhn (1912–2005) discovered the first tricyclic antidepressant in the process of improvement of the efficacy of chlorpromazine in conjunction with the Geigy Pharmaceutical Company. He also coined the term 'thymoleptic' (Kuhn 1957, 1958). In 1988, fluoxetine, the first SSRI, was introduced. It was developed at Eli Lilly and Company in the early 1970s by Bryan Molloy, Klaus Schmiegel, David Wong and others. In spite of a long-lasting recent debate, the efficacy of antidepressants in the treatment of unipolar depression is no longer a matter of dispute (Fountoulakis et al. 2013b; Fountoulakis and Moller 2012; Sartorius et al. 2007).

Currently there are several classes of antidepressants including the selective serotonin reuptake inhibitors (SSRIs), the serotonin–norepinephrine reuptake inhibitors (SNRIs), the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs).

The main neurotransmitter pathway through which antidepressants seem to exert their beneficial effect is that of serotonin. Pure noradrenergic action is unlikely to be sufficient to produce an antidepressant effect; however, double-acting agents (which affect both serotonin and noradrenaline pathways) might be more efficacious in comparison to purely serotonergic agents but also with more adverse effects.

The most common adverse effects include nausea, increased appetite and weight gain, loss of sexual desire and other sexual problems (e.g. erectile dysfunction and decreased ability to achieve orgasm), fatigue and drowsiness, insomnia, dry mouth, blurred vision, constipation, dizziness, agitation, irritability, anxiety, sexual problems and hyperprolactinaemia. Serotonergic syndrome is a potentially lethal event. Treatment with antidepressants also might induce suicidal thoughts, but no completed suicide has been attributed to treatment with antidepressants. Some agents after abrupt stop of treatment might cause withdrawal symptoms which persist for no more than 1–2 weeks.

Although the teratogenic risk is low with antidepressants, SSRI use in pregnancy has been associated with an increased risk of spontaneous abortion, preterm birth and low birth weight (Malm 2012; Rahimi et al. 2006).

The usefulness of antipsychotics in the treatment of bipolar depression is a matter of continuous debate (Pacchiarotti et al. 2013). It is interesting that some data suggest that norepinephrine activity is necessary for an antidepressant to act in bipolar depression; still this very activity increases the risk for the patients to switch to mania or hypomania (Fountoulakis et al. 2012c).

16.2 Evidence-Based Treatment

The literature was searched and the text that follows is updated through August 2014. The method which was followed in order to rank the agents according to the data is a modification of the PORT method, and it is shown in detail in Table 16.1. However the lack of data did not make this feasible for all facets and aspects of the disease. Thus, also a binomial classification was also made with agents being efficacious ('yes') or proven not to be ('neg'). It is disappointing that for the majority of agents vs. aspects, there are no data to refer to (–). All the evidence-based data are shown in Tables 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, and 16.9.

Table 16.1 Description of the method which was followed to rank the data in the present book chapter. Essentially it is a modified PORT method for the grading of data, on the basis of efficacy alone

Level A	Good research-based evidence, supported by at least 1 placebo-controlled study of sufficient magnitude. If there are non-placebo trials controlled with a comparator and with different results, the placebo controlled is the only taken into consideration
Level B	Fair research-based evidence, from at least one randomised, double-blind controlled trial which, however, fails to fulfil all the criteria above (e.g. very small sample size or no placebo control)
Eq	Equivocal data, that is, one positive and one negative RCT, only failed but not negative studies, positive meta-analysis, etc. Equivocal data as a level is superior to level C
Level C	At least one double-blind study with placebo or not, with a special design (e.g. ABA, discontinuation studies, etc.) or at least one open-label study with comparator or prospective open-label study or two prospective open-label studies with >10 participants
Level D	Recommendation based on prospective case studies with a minimum of 10 patients or large-scale retrospective chart analyses and support by expert opinion
Neg	Negative data

Table 16.2 Summary table of monotherapy data for the treatment of acute bipolar mania

Agent/modality (alphabetical order)	Effect start day	Overall	Core manic	Depressive	Psychotic	Agitation
Amisulpride	–	C	–	–	–	–
Aripiprazole	2–4	A	–	Yes	Yes	–
Asenapine	2	A	–	Eq	–	–
Carbamazepine	14	A	Yes	Yes	–	–
Cariprazine	4	A	Yes	No	–	–
Chlorpromazine	–	B	–	–	–	–
Clozapine	–	C	–	–	–	–
ECT	–	C	–	–	–	–
Eslicarbazepine	–	Neg	–	–	–	–
Gabapentin	–	Neg	–	–	–	–
Haloperidol	4	A	No	No	Yes	Yes
Lamotrigine	–	Neg	–	–	–	–
Licarbazepine	–	Neg	–	–	–	–
Lithium	7	A	Eq	No	No	–
Loxapine inhalant	–	–	–	–	–	Yes
Olanzapine	2–7	A	Yes	Yes	Yes	Yes
Oxcarbazepine	–	C	–	–	–	–
Paliperidone	2	A	–	–	–	–
Perphenazine	–	–	–	–	–	–
Quetiapine	4	A	–	Yes	Yes	–
Risperidone	3	A	–	Yes	Yes	–
Tamoxifen	5	A	Yes	No	Yes	–
TMS	–	C	–	–	–	–
Topiramate	–	Neg	–	–	–	–
Valproate	5–15	A	No	No	–	Yes
Verapamil	–	Neg	–	–	–	–
Ziprasidone	2	A	Yes	Eq	Yes	–

– no data, *Neg* negative data

Table 16.3 Summary table of data for the combination treatment of acute bipolar mania

Agent/modality (alphabetical order)	MS	Cbz	Lam	Li	Val	FGAs
Amisulpride	–	–	–	–	–	–
Aripiprazole	A	–	–	A	A	–
Asenapine	A	–	–	A	A	–
Carbamazepine	–	–	–	–	–	–
Cariprazine	–	–	–	–	–	–
Chlorpromazine	–	–	–	–	–	–
Clozapine	–	–	–	–	–	–
ECT	–	–	–	–	–	–
Eslicarbazepine	–	–	–	–	–	–
Gabapentin	Neg	–	–	–	–	–
Haloperidol	–	B	–	A	A	–
Lamotrigine	–	–	–	–	–	–
Licarbazepine	–	–	–	–	–	–
Lithium	–	B	–	–	–	–
Loxapine inhalant	–	–	–	–	–	–
Olanzapine	Yes	Neg	–	A	A	–
Oxcarbazepine	–	–	–	B	–	–
Paliperidone	Neg	–	–	Neg	Neg	–
Perphenazine	–	–	–	–	–	–
Quetiapine	A	–	–	A	A	–
Risperidone	–	A	–	A	A	–
Tamoxifen	–	–	–	–	–	–
TMS	–	–	–	–	–	–
Topiramate	Neg	–	–	–	–	–
Valproate	–	–	–	–	–	Yes
Verapamil	–	–	–	–	–	–
Ziprasidone	A	–	–	Neg	–	–

– no data, *Neg* negative data

16.2.1 Acute Mania

16.2.1.1 Monotherapy

A summary of monotherapy data for the treatment of acute mania is shown in Table 16.2.

16.2.1.1.1 Lithium

Although the first placebo-controlled study concerning the efficacy of lithium against acute mania was conducted in 1971 (Stokes et al. 1971), the first properly done study was in 179 hospitalized, acutely manic patients in academic settings across the USA, appeared as late as 1994, although lithium was available with a label for the treatment of BD already since decades. In that first 3-week study, the

Table 16.4 Summary table of monotherapy data for the treatment of acute bipolar depression overall and in BD-I and BD-II patients

Agent/modality (alphabetical order)	Monotherapy	BD-I	BD-II	Depressive core
Amisulpride	–	–	–	–
Aripiprazole	Eq	–	–	–
Asenapine	–	–	–	–
Bupropion	–	–	–	–
Carbamazepine	Eq	–	–	–
Chlorpromazine	–	–	–	–
Clozapine	–	–	–	–
Desipramine	–	–	–	–
Escitalopram	C	–	C	–
ECT	D	–	–	–
Fluoxetine	A	–	–	–
Gabapentin	Neg	–	–	–
Haloperidol	–	–	–	–
Imipramine	C	–	–	–
Ketamine	–	–	–	–
Lamotrigine	Eq	–	Eq	Yes
Levetiracetam	–	–	–	–
Lithium	Neg	–	Eq	–
Lurasidone	A	–	–	Yes
Olanzapine	Eq	Eq	–	Eq
OFC	A	Yes	–	Yes
Oxcarbazepine	–	–	–	–
Paliperidone	–	–	–	–
Paroxetine	Neg	No	No	–
Perphenazine	–	–	–	–
Quetiapine	A	Yes	Yes	Yes
Risperidone	–	–	–	–
Sleep deprivation	–	–	–	–
Tamoxifen	–	–	–	–
TMS	–	–	–	–
Topiramate	–	–	–	–
Valproate	Eq	Eq	–	Eq
Venlafaxine	–	–	–	–
Ziprasidone	Neg	–	–	–
CBT	–	–	–	–
Psychoeducation	–	–	–	–

– no data, *Neg* negative data

Table 16.5 Summary table of data for the combination treatment of acute bipolar depression

Agent/modality (alphabetical order)	MS	Cbz	Lam	Li	Val
Amisulpride	–	–	–	–	–
Aripiprazole	–	–	–	Neg	–
Asenapine	–	–	–	–	–
Bupropion	Neg	Neg	–	Neg	Neg
Carbamazepine	–	–	–	–	–
Chlorpromazine	–	–	–	–	–
Clozapine	–	–	–	–	–
Desipramine	–	–	–	–	–
Escitalopram	–	–	–	–	–
ECT	–	–	–	–	–
Fluoxetine	–	–	–	–	–
Gabapentin	–	–	–	–	–
Haloperidol	–	–	–	–	–
Imipramine	–	–	–	Neg	–
Ketamine	–	–	–	B	B
Lamotrigine	–	–	–	A	–
Levetiracetam	Neg	–	–	–	–
Lithium	–	–	A	–	–
Lurasidone	–	–	–	A	A
Olanzapine	–	–	–	–	–
OFC	–	–	–	–	–
Oxcarbazepine	–	–	–	B	–
Paliperidone	–	–	–	–	–
Paroxetine	Neg	Neg	–	Neg	Neg
Perphenazine	–	–	–	–	–
Quetiapine	–	–	–	–	–
Risperidone	–	–	–	–	–
Sleep deprivation	–	–	–	–	–
Tamoxifen	–	–	–	–	–
TMS	–	–	–	–	–
Topiramate	–	–	–	–	–
Valproate	–	–	–	–	–
Venlafaxine	–	–	–	–	–
Ziprasidone	Neg	–	Neg	Neg	Neg
CBT	–	–	–	–	–
Psychoeducation	–	–	–	–	–

– no data, *Neg* negative data

Table 16.6 Summary table of monotherapy data for the maintenance treatment phase

Agent/modality (alphabetical order)	Index episode	Enriched sample	Manic	Depressive	Mixed
Amisulpride	–	–	–	–	–
Aripiprazole	m[a]	Yes	Yes	No	–
Asenapine	–	–	–	–	–
Carbamazepine	–	–	–	–	–
Chlorpromazine	–	–	–	–	–
Clozapine	–	–	–	–	–
Electroconvulsive therapy	–	–	–	–	–
Fluoxetine	d	Yes	–	Eq	–
Gabapentin	–	–	–	–	–
Haloperidol	–	–	–	–	–
Imipramine	d	?	–	Eq	–
Lamotrigine	m/d	Yes	Yes	Yes	–
Lithium	m/d	No	Yes	Yes	–
N-acetyl cysteine	d	Yes		–	–
Olanzapine	m	Yes/no	Yes	Yes	Yes
Olanzapine–fluoxetine combination	–	–	–	Yes	–
Oxcarbazepine	–	–	–	–	–
Paliperidone	m	Yes	Yes	No	–
Paroxetine	–	–	–	–	–
Perphenazine	m	Yes	–	–	–
Phenytoin	euth	No	–	–	–
Pramipexole	euth	No	–	–	–
Quetiapine	m/d	Yes	Yes	Yes	–
Risperidone, long-acting injectable	m	Yes	Yes	No	–
Sertraline	–	–	–	–	–
Sleep deprivation	–	–	–	–	–
Tamoxifen	–	–	–	–	–
Transcranial magnetic stimulation	–	–	–	–	–
Topiramate	–	–	–	–	–
Valproate	m	Yes	Neg	Eq	–
Ziprasidone	m	Yes	–	–	–
CBT	d	No	–	–	–
Psychoeducation	m/d	No	–	–	–

Index episode also refers to data presented in Tables 16.7, 16.8, and 16.9
m mania/mixed, *d* depression, *m/d* both mania and depression, *UT* treatment as usual, *MS* mood stabilizers
[a]Aripiprazole is efficacious with a manic but not mixed index episode

Table 16.7 Summary table of combination data for the maintenance treatment phase and also concerning the maintenance treatment of rapid cycling patients and the risk for switching to the opposite pole

Agent/modality (alphabetical order)	TAU	Cbz	Lam	Li	Val	Rapid cycling	Switch
Amisulpride	–	–	–	–	–	–	–
Aripiprazole	–	–	Neg	Yes	Yes	Yes	No
Asenapine	–	–	–	–	–	–	No
Carbamazepine	–	–	–	Neg	–	Li + cbz	No
Chlorpromazine	–	–	–	–	–	–	–
Clozapine	–	–	–	–	–	–	–
Electroconvulsive therapy	–	–	–	–	–	–	–
Fluoxetine	–	–	–	–	–	–	No
Gabapentin	–	Yes	–	Yes	Yes	–	–
Haloperidol	–	–	–	–	–	–	Eq
Imipramine	–	–	–	Neg		–	Yes
Lamotrigine	–	–	–	Neg	Neg	Neg	No
Lithium	–	–	Neg	–	–	Li + cbz	No
N-acetyl cysteine	Neg	–	–	–	–	–	–
Olanzapine	–	–	–	Eq	Eq	–	No
Olanzapine–fluoxetine combination	–	–	–	–	–	–	No
Oxcarbazepine	–	–	–	Neg	–	–	–
Paliperidone	–	–	–	–	–	–	No
Paroxetine	–	–	–	–	Yes	–	No
Perphenazine	–	Neg	–	Neg	Neg	–	Yes
Phenytoin	Yes	–	–	–	–	–	–
Pramipexole	Neg	–	–	–	–	–	–
Quetiapine	–	–	–	m/d	m/d	Quet + val/li	No
Risperidone, long-acting injectable	m	–	–	–	–	RLAI + TAU	No
Sertraline	–	–	–	–	Yes	–	No
Sleep deprivation	–	–	–	–	–	–	–
Tamoxifen	–	–	–	–	–	–	–
Transcranial magnetic stimulation	–	–	–	–	–	–	–
Topiramate	–	–	–	–	–	–	–
Valproate	–	–	–	–	–	–	No
Ziprasidone	–	m	–	M	m	–	No
CBT	d	–	–	–	–	–	–
Psychoeducation	m/d	–	–	–	–	–	–

m mania/mixed, *d* depression, *m/d* both mania and depression, *TAU* treatment as usual, *MS* mood stabilizers

Table 16.8 Summary table of data for the treatment of acute mixed episodes and acute bipolar mania/mixed in rapid cycling patients

Agent/modality (alphabetical order)	Mixed episodes		
	Manic component	Depressive component	Rapid cycling
Amisulpride	–	–	–
Aripiprazole	Yes	Yes	Yes
Asenapine	Yes	–	–
Carbamazepine	Yes	Yes	–
Cariprazine	–	–	–
Chlorpromazine	–	–	–
Clozapine	–	–	–
ECT	–	–	–
Eslicarbazepine	–	–	–
Gabapentin	–	–	–
Haloperidol	–	–	–
Lamotrigine	–	–	–
Licarbazepine	–	–	–
Lithium	No	–	Neg[a]
Loxapine inhalant	–	–	–
Olanzapine	Yes	Eq	Yes
Oxcarbazepine	–	–	–
Paliperidone	Yes	No	–
Perphenazine	–	–	–
Quetiapine	Eq	–	No
Risperidone	Yes	–	–
Tamoxifen	–	–	–
TMS	–	–	–
Topiramate	–	–	–
Valproate	Yes	Eq	Neg[a]
Verapamil	–	–	–
Ziprasidone	Eq	Eq	–

– no data, *Neg* negative data
[a]For the combination lithium plus valproate

efficacy and safety of lithium (serum levels below 1.5 mmol/l; $N=36$) and divalproex (serum levels below 150 μg/ml; $N=69$) were compared to placebo ($N=74$). Half of them were previously nonresponsive to lithium, and none had previously received valproate; thus, the study sample was enriched in favour of divalproex. After 3 weeks, both treatment arms manifested a higher change in MRS in comparison to placebo, and this change was significant since day 15 for both agents. Unfortunately the results are reported only through a chart, and no exact means and standard deviations are available. Interestingly, the analysis of separate items of the MRS revealed that divalproex but not lithium had a beneficial effect on the core manic symptoms. The response rate was higher for lithium and divalproex in

Table 16.9 Summary table of data for the treatment of comorbid anxiety in bipolar depressed patient, the efficacy against acute bipolar depression in rapid cycling patients and the risk of switch to mania/hypomania

Agent/modality (alphabetical order)	Anxiety	Rapid cycling	Switch risk
Amisulpride	–	–	–
Aripiprazole	–	–	No
Asenapine	–	–	–
Bupropion	–	–	No
Carbamazepine	–	–	–
Chlorpromazine	–	–	–
Clozapine	–	–	–
Desipramine	–	–	Yes
Escitalopram	–	–	No
ECT	–	–	–
Fluoxetine	–	–	–
Gabapentin	–	–	–
Haloperidol	–	–	–
Imipramine	–	–	Yes
Ketamine	–	–	–
Lamotrigine	–	–	–
Levetiracetam	–	–	–
Lithium	Neg	Eq	–
Lurasidone	Yes	–	–
Olanzapine	–	–	No
OFC	–	–	No
Oxcarbazepine	–	–	–
Paliperidone	–	–	–
Paroxetine	Yes	No	No
Perphenazine	–	–	–
Quetiapine	Yes	Yes	No
Risperidone	No	–	–
Sleep deprivation	–	–	–
Tamoxifen	–	–	–
TMS	–	–	–
Topiramate	–	–	–
Valproate	Eq	Neg	–
Venlafaxine	–	–	Yes
Ziprasidone	–	–	–
CBT	–	–	–
Psychoeducation	–	–	–

– no data, *Neg* negative data

comparison to placebo (49 % vs. 48 % vs. 25 %; $p=0.025$). In spite of the fact that half of the patients were previously unresponsive to lithium, no inferiority of lithium in comparison to divalproex was observed. Fewer patients in the divalproex arm dropped out (61 % vs. 48 % vs. 64 %). Dropouts because of lack of efficacy were fewer in the two treatment arms in comparison to placebo (33 % vs. 30 % vs. 51 %), while dropouts because of adverse events were more frequent with lithium (11 % vs. 6 % vs. 3 %). The most frequent adverse events with lithium were asthenia, constipation, dizziness, nausea, fever, twitching and vomiting (Bowden et al. 1994). A post hoc analysis of the previous study confirmed the efficacy of lithium in classic manic but not mixed patients. All other effects were negative (Swann et al. 1997). An international multicentre 12-week RCT (3 weeks with placebo) in 302 acutely manic BD patients compared lithium (target serum levels 0.6–1.4 mEq/l; $N=98$) vs. quetiapine IR (flexibly dosed up to 800 mg/day; $N=107$) and vs. placebo ($N=97$). The improvement in YMRS score was significantly greater for lithium, and quetiapine IR in comparison to placebo at week 3 (−15.2 vs. −14.6 vs. −6.7; $p<0.001$) was present already during day 7 and persisted throughout the duration of the study. Significantly more lithium- and quetiapine IR-treated patients were responders in comparison with placebo patients at week 3 (53.1 % vs. 53.3 % vs. 27.4 %; $p<0.001$), and the picture was similar concerning the remission rates (49 % vs. 46.7 % vs. 22.1 %; $p<0.001$). The picture was similar concerning remission rates. While the quetiapine IR data concerning all individual YMRS items were reported, this was not reported also for lithium. Quetiapine IR but not lithium significantly improved the PANSS positive subscale, and both improved the activation and the aggression subscale. The effect on the negative subscale was not reported. Both medications significantly improved the MADRS score, but lithium achieved this only at endpoint while quetiapine IR already at day 21. Fewer patients in the lithium and quetiapine IR groups dropped out from the study compared with the placebo group (31.6 % vs. 32.7 % vs. 63.9 %). Also fewer of them dropped out because of lack of efficacy (12.2 % vs. 14.9 % vs. 39.2 %), while the dropout rate because of adverse events was similar among groups (6.1 % vs. 6.5 % vs. 4.1 %). The most common adverse events for lithium were tremor and insomnia (Bowden et al. 2005b). The third was an international multicentre study (PDMD-004), and it included 444 acutely manic or mixed BD patients and studied the efficacy and safety of lithium (1,500 mg/day; $N=113$) vs. topiramate (200 mg/day; $N=110$ or 400 mg/day; $N=110$) vs. placebo ($N=111$). At week 3, lithium-treated patients manifested significantly more reduction in their YMRS scores in comparison both to the topiramate arms and to placebo (−12.9 vs. −5.8 vs. −6.2 vs. −7.7; $p<0.001$). The withdrawal rate was similar among groups (26–29 %) with no difference concerning the cause. The fourth study was PDMD-008 which compared 1,500 mg of lithium daily ($N=114$) vs. 400 mg topiramate daily ($N=116$) vs. placebo ($N=112$) in 342 BD-I acutely manic or mixed patients. The withdrawal rate was 18 % for lithium and 13 % for placebo, with lithium-treated patients dropping out more frequently because of adverse effects and placebo-treated patients because of lack of efficacy. At week 3, lithium-treated patients manifested significantly more reduction in their YMRS scores in comparison to placebo (−13.8 vs, −8.4; $p<0.001$).

These two studies were not published independently but only together with the other two negative topiramate trials in an exploratory analysis in search of a potential efficacy signal. That analysis pooled all data from these four studies and reported that the percentage of responders at week 3 was 37 % for lithium vs. 22 % for placebo. Again there was no effect of lithium on the MADRS score. Nausea, diarrhoea, dizziness and weight gain were the more frequent side effects of lithium treatment (Kushner et al. 2006). A fourth 12-week (3 weeks with placebo) multicentre US study in 480 acutely manic or mixed patients (rapid cycling excluded) investigated lithium (900–1,500 mg/day; $N=160$) vs. aripiprazole (15–30 mg/day; $N=155$) vs. placebo ($N=165$). Both lithium and aripiprazole demonstrated significantly greater improvement than placebo in YMRS score at week 3 (−12.0 vs. −12.6 vs. −9.0; $p<0.005$), and the improvement was evident since week 1 for lithium and since day 2 for aripiprazole and continued for all the study period. The response rate was significantly higher in both the lithium and the aripiprazole groups in comparison to placebo at week 3 (45.8 % vs. 46.8 % vs. 34.4 %; $p<0.05$). A similar picture was evident concerning the remission rates (40 % vs. 40.3 % vs. 28.2 %). No effect on PANSS total or MADRS was observed for lithium. No results concerning the PANSS positive and negative subscales were reported. The dropout rate was similar between groups (51 % vs. 53 % vs. 53 %) at week 3. The dropout rate for lithium because of lack of efficacy was between that of aripiprazole and placebo (16 % vs. 6 % vs. 22 %), while more patients in the two medication arms dropped out because of adverse events in comparison to placebo (13 % vs. 15 % vs. 8 %). The most common adverse events with lithium were nausea, headache, constipation and tremor (Keck et al. 2009).

Overall, the literature suggests that lithium is effective for the treatment of acute manic episodes with or without mixed features. It has four positive studies (Bowden et al. 1994, 2005b; Kushner et al. 2006; Keck et al. 2009). The effect size for response has the magnitude of NNT equal to 5–6 at week 3, and the therapeutic effect appears after 7 days of treatment, that is, later in comparison to antipsychotics. There are limited data which dispute the effect of lithium on the core symptoms of mania. Its effect specifically on mixed episodes is unknown. Probably there is no therapeutic effect on concomitant depressive and psychotic symptoms. The most common adverse events with lithium were nausea, vomiting, dizziness headache, insomnia, asthenia, constipation, diarrhoea, tremor and weight gain.

16.2.1.1.2 Antiepileptics

Valproate

Limited data concerning the efficacy of valproate in acute mania exist from earlier studies which utilized very small study samples and a very different study design. Fourteen patients from these early studies were tested under double-blind conditions, and ten of them (71.4 %) were reported to have significantly improved (McElroy et al. 1989). Such an early study utilized an ABA design in five acutely ill manic patients who were treated with valproate 1.8–3.8 g/day (serum concentrations 50–100 μg/ml). These authors reported that in four cases a marked

improvement (over 60 %) was observed within 3–15 days. They also reported that another seven patients with frequently recurrent episodes of a manic or maniform schizoaffective psychosis, previously unresponsive to lithium prophylaxis, were chronically treated with valproate in combination with low doses of lithium (one case only with valproate). Over an observation period of 1.5–3 years, none of the patients suffered from a relapse (Emrich et al. 1980, 1981).

As in the case of lithium, the first study with modern methodology on the efficacy and safety of valproate in the treatment of acute mania took place only in 1991. It was conducted in a small study sample which was enriched for lithium refractoriness and included 36 acutely manic patients (refractory or intolerant to lithium). Valproate serum concentrations were between 50 and 100 mg/l. The patients randomized to valproate ($N=17$) manifested a 54 % reduction in their YMRS in comparison to 5 % in patients of the placebo group ($N=19$). The treatment effect was present 1–4 days after achieving therapeutic serum concentrations (>50 mg/l). Fewer patients under valproate dropped out because of lack of efficacy (24 % vs. 63 %) but more because of adverse events (12 % vs. 5.3 %). There was no difference in the adverse effects profile between the treatment arms (Pope et al. 1991). Another 3-week study in 179 hospitalized, acutely manic patients in academic settings across the USA investigated the efficacy and safety of divalproex (serum levels below 150 µg/ml; $N=69$) and lithium (serum levels below 1.5 mmol/l; $N=36$) vs. placebo ($N=74$). Half of them were previously nonresponsive to lithium, and none had previously received valproate; thus, the study sample was enriched in favour of divalproex. After 3 weeks, both treatment arms manifested a higher change in MRS in comparison to placebo, and this change was significant since day 15 for both agents. Unfortunately the results were reported only through a chart, and no exact means and standard deviations are available. Interestingly, the analysis of separate items of the MRS revealed that divalproex but not lithium had a beneficial effect on the core manic symptoms. The response rate was higher for divalproex and lithium in comparison to placebo (48 % vs. 49 % vs. 25 %; $p=0.025$). In spite of the fact that half of patients were previously unresponsive to lithium, no superiority of divalproex was observed. Fewer patients in the divalproex arm dropped out (48 % vs. 61 % vs. 64 %). Dropouts because of lack of efficacy were fewer in the two treatment arms in comparison to placebo (30 % vs. 33 % vs. 51 %), while dropouts because of adverse events were more frequent with lithium (6 % vs. 11 % vs. 3 %). The most frequent adverse events for divalproex were asthenia, constipation, dizziness, nausea, twitching and vomiting (Bowden et al. 1994). A post hoc analysis of the previous study did not find any beneficial effect for divalproex either in classic or in mixed manic patients (Swann et al. 1997). Another multicentre study in 377 hospitalized patients suffering from an acute manic or mixed episode was conducted in the USA and investigated the efficacy and safety of divalproex sodium extended release (divalproex ER; $N=187$) against placebo ($N=177$). The target was serum valproate concentrations of 85–125 µg/ml. Patients receiving divalproex ER manifested more improvement in the MRS scores at week 3 (−11.5 vs.−9.0; $p=0.01$), and the difference was observable already at day 5. At week 3, 48 % of divalproex-treated patients were responders in comparison to 34 % in the placebo group

($p=0.01$). One problematic finding of this study is that divalproex ER did not differ from placebo in its effect on core manic symptoms like elevated mood, pressured speech and grandiosity. More patients in the divalproex ER group discontinued because of adverse events (10 % vs. 3 %), while less discontinued because of lack of efficacy (13 % vs. 26 %) in comparison to placebo. The overall discontinuation rates were comparable (58 % vs. 52 %). The most frequent side effects associated with treatment with divalproex ER were somnolence, dizziness and gastrointestinal complaints (Bowden et al. 2006). Another international multicentre study in 521 acutely manic or mixed patients evaluated the efficacy and safety of divalproex (500–2,500 mg/day; $N=201$) vs. olanzapine (5–20 mg/day; $N=215$) vs. placebo ($N=105$). At week 3, divalproex-treated patients were not better than placebo in contrast to olanzapine-treated patients in terms of change in their YMRS scores (−8.2 vs. −9.4 vs. −7.4). There was no difference in the MADRS score change between the medication arms and placebo. The response rates did not differ between the medication arms and placebo (40.3 % vs. 40.8 % vs. 31.3 %) and neither did the remission (40.3 % vs. 42.8 % vs. 35.4 %) nor the dropout rates (26 % vs. 24.9 % vs. 26.6 %). Overall, divalproex did not differ from placebo, and the negative findings persisted throughout the study. It is interesting that while 35.4 % (at 3 weeks) to 57.1 % (at 12 weeks) had valproate plasma concentrations lower than the recommended valproate therapeutic range, the YMRS scores of these patients were lower than those of patients with valproate concentrations above or within range. Patients treated with divalproex had significant decreases in leukocytes and platelets compared with olanzapine at week 12 (Tohen et al. 2008b). The next study was a small RCT which took place in a single academic setting in the USA and included a heterogeneous sample consisting of ambulatory bipolar spectrum disorder patients and patients with moderate-to-severe hypomanic or mild manic symptoms (hypomania/mild mania). Sixty patients were randomized to divalproex ER (15–30 mg/kg/day) or placebo. Probably due to the small study sample, no difference was detected in any of the outcome measures or the adverse effects between the treatment groups. There was no difference in the dropout rate between divalproex ER and placebo (57 % vs. 50 %) although in terms of reason, lack of efficacy was twofold higher in the placebo group (24 % vs. 47 %). There are a number of methodological and reporting issues pertaining to this study (McElroy et al. 2010a). The last was a failed multicentre study conducted in the USA and randomized 225 acutely manic or mixed patients to receive either divalproex ER ($N=147$) or placebo ($N=78$). The mean dose of divalproex ER was 2,211 mg/day, and the mean maximum serum valproic acid serum concentration was 77.9 μg/ml. At week 3, there was no difference in the outcome, the adverse effects or the dropout rate between the two treatment groups. The dropout rate was exceptionally high for a 3-week trial and similar for both groups (83 % vs. 80 %) (Hirschfeld et al. 2010).

Overall the data support the usefulness of valproate against acute mania. However it should be noted that a number of issues exist and future studies are needed to clarify them. Valproate has three positive (Pope et al. 1991; Bowden et al. 1994, 2006) and two failed (Tohen et al. 2008b; Hirschfeld et al. 2010) studies. Its effect on psychotic symptoms is unknown, and there seems to be no effect on concomitant

depressive symptoms. It is problematic that the most recent and rigorously conducted studies on large samples either failed to support its overall efficacy or failed to find an effect on the core clinical features of acute mania. The NNT for response is probably around ten, and the therapeutic effect is present after 5–15 days. It is important to note that although the dosages utilized in these studies were somewhat higher than those usually used in everyday clinical practice (15–30 mg/kg/day which for a 75 k person correspond to 1,125–2,250 mg/day), they hardly achieved the target serum concentrations (50–100 μg/ml). On the other hand, the adverse effect profile was mild and without significant difference from the placebo group. The most frequent adverse events were somnolence, nausea, dizziness, asthenia, constipation, twitching and vomiting. Decreases in leukocytes and platelets have also been reported.

Carbamazepine

The first study on carbamazepine was published in 1980 and reported that 7 out of 9 manic and 5 out of 13 depressed patients had a partial to marked response when administered with carbamazepine (600–1,600 mg/day, blood levels 8–12 μg/ml). Also that several patients showed relapses when placebo was introduced and improvement when carbamazepine was reinstituted (Ballenger and Post 1980). Another study which utilized the ABAB design included 19 acutely manic patients and utilized carbamazepine in doses averaging 1,240 mg/day (blood levels 10.4 ± 2.2 μg/ml). These authors reported a rapid clinical improvement in 12 patients (63.2 %), and response was related to significantly more manic symptoms during the baseline placebo period, more dysphoric picture and rapid cycling. That study suggested that several predictors of poor response to lithium carbonate (manic severity, anxiety and dysphoria, rapid cycling and negative family history) may be associated with good response to carbamazepine (Post et al. 1987). The first multicentre US study on carbamazepine which conducted with a modern methodology utilized 204 acutely manic or mixed patients and was published in 2004. It was a 3-week RCT and compared carbamazepine extended release (carbamazepine ER; 400–1,600 mg/day; mean plasma level 8.9 μg/ml; $N = 101$) vs. placebo ($N = 103$). Half of the patients dropped out. Carbamazepine ER exhibited a significant reduction in YMRS scores ($p = 0.032$), and this was evident since week 2. Unfortunately the results were published only in the form of charts, and thus precise mean and standard deviations of change scores are not available. More patients under carbamazepine ER were responders (41.5 % vs. 22.4 %; $p = 0.007$). It is unclear whether it improved mixed patients also, and not only purely manic, because of a large placebo effect in the mixed group. There was no effect on the depressive score as measured by the HAM-D in the manic patients; however, there was a significant improvement in the mixed patients. The most frequent adverse events related to carbamazepine were dizziness, nausea and somnolence (Weisler et al. 2004). The second multicentre international study (USA and India) in 239 hospitalized acutely manic or mixed patients compared carbamazepine ER (400–1,600 mg/day; $N = 122$) vs. placebo ($N = 117$). Numerically fewer patients in the carbamazepine arm dropped out (34.4 % vs. 45.3 %) with more patients in the placebo arm discontinuing due to lack

of efficacy (6.6 % vs. 23.1 %; $p<0.001$), while the dropout rate because of adverse events was similar in the two arms. Carbamazepine ER exhibited a significant reduction in YMRS scores since day 7 ($p<0.05$); however, again the publication of results is incomplete. The adverse events related to the carbamazepine ER arm included dizziness (39.3 %), somnolence (30.3 %) and nausea (23.8 %). Carbamazepine-treated patients also experienced a significant increase in total cholesterol, composed of increases in both high-density and low-density lipoproteins (Weisler et al. 2005). The pooled data of the 443 patients which took part in the two above-mentioned studies suggested that there was a trend less patients in the carbamazepine ER group to drop out in comparison to the placebo arm (42 % vs. 50 %; $p=0.087$). Significantly less patients under carbamazepine ER dropped out because of lack of efficacy (10 % vs. 22 %; $p<0.001$). At week 3 carbamazepine ER was related to significantly more reduction in the YMRS score in comparison to placebo (for manic episodes, $p<0.0001$; for mixed, $p<0.01$). There was also a significant reduction in the HAM-D scores of mixed patients (−4.8 vs. −2.3; $p<0.05$). More patients under carbamazepine ER patients experienced an adverse event (90 % vs. 64 %), and more of them dropped out because of adverse events (10.8 % vs. 5.5 %) (Weisler et al. 2006).

Finally, there is a 12-week double-blind, randomized, placebo-controlled study from China in 111 patients with acute mania which were randomized to carbamazepine (300–800 mg/day; $N=43$) vs. carbamazepine plus the herbal Free and Easy Wanderer Plus (FEWP; 36 g/day; $N=46$) vs. placebo ($N=22$). At endpoint both carbamazepine arms produced significantly greater improvement on YMRS score, and the improvement was present already at week 4, but they did not differ from each other (−22.9 vs. −25.4 vs. −17). In terms of response rates, more patients in the carbamazepine arms were superior to placebo (87.8 % vs. 93 % vs. 57.1 %, $p=0.012$). Interestingly, although there was no difference between the two carbamazepine groups concerning the carbamazepine dosage, fewer patients under the combination dropped out (25.6 % vs. 13 % vs. 40.9 %), and this was also true concerning dropout because of lack of efficacy (7 % vs. 4.3 % vs. 27.3 %). Depressed and manic patients were pooled for the analysis of adverse events, and the adverse events occurring in over 5 % of the patients in any treatment group were dizziness, laboratory testing abnormality, skin rash, headache, fatigue, blurred vision, somnolence and nausea. Compared to carbamazepine monotherapy, patients in the combination therapy had a lesser incidence of dizziness (18.2 % vs. 7.9 %; $p=0.069$) and fatigue (9.1 % vs. 1.1 %; $p=0.038$). No difference in the incidence of other adverse events was found between the combination therapy and CBZ monotherapy. Although this study supports the efficacy of carbamazepine during the acute manic phase, the low carbamazepine dosage, in combination with the possible dramatic reduction of carbamazepine levels when co-administered with FEWP, plus the unusually high response rate even in the placebo group and the unusually low dropout rate, makes conclusions difficult (Zhang et al. 2007).

Overall the data concerning the efficacy and safety of carbamazepine at dosages 400–1,600 mg/day and mean plasma level 8.9 μg/ml are robust, with three positive studies (Weisler et al. 2004, 2005; Zhang et al. 2007) and suggest an NNT of

approximately 5 for response. Response starts since week 2. It is unknown whether carbamazepine has a beneficial effect on the core manic symptoms. There seems to be a beneficial effect on concomitant depressive symptoms only in mixed patients but not in purely manic, and the efficacy against psychotic symptoms is unknown. The most frequent adverse events related to carbamazepine treatment were dizziness, nausea, somnolence and an increase in total cholesterol which was composed of increases in both high-density and low-density lipoproteins.

Other Antiepileptics

Recently two 3-week multicentre, double-blind, randomized, placebo-controlled studies in acute mania were conducted concerning eslicarbazepine. The first one (BIA-2093-203) utilized a dose titrated by response (600–1,800 mg or 800–2,400 mg/day) and it was negative, while the second (BIA-2093-204) utilized fixed doses of 600, 1,200 and 1,800 mg/day, and it was a failed trial (Robertson et al. 2010). Three other also unpublished RCTs (NCT00107926, NCT00107939 and NCT00099229) concerning the racemic mixture licarbazepine were also negative.

There are two unpublished negative trials concerning lamotrigine against acute manic episodes (SCAA2008/GW609 and SCAA2009/GW610). The SCAA2008/GW609 study had 3-week duration and investigated the efficacy and safety of lamotrigine (50 mg/day; $N=84$) vs. lithium (titrated to a serum level of 0.8–1.3 mEq/l; $N=36$) vs. placebo ($N=95$). This study was generally underpowered. The SCAA2009/GW610 was a 6-week study and investigated lamotrigine (200 mg/day; $N=74$) vs. lithium (titrated to a serum level of 0.7–1.3 mEq/l; $N=77$) vs. placebo ($N=77$). In this later study the MRS scores were significantly reduced in patients receiving lithium vs. placebo ($p=0.05$). Lamotrigine was not associated with worsening manic symptoms in these trials (Goldsmith et al. 2003). One additional small RCT evaluated the efficacy and safety of lamotrigine (max 500 mg/day) and gabapentin (max 4,800 mg/day) monotherapy vs. placebo in 31 patients with refractory bipolar and unipolar mood disorders. At week 6, 52 % of patients under lamotrigine and 26 % under gabapentin were responders vs. 23 % in the placebo group. Lamotrigine differed significantly from placebo ($p=0.022$) but not gabapentin ($p=0.08$). Both agents were generally well tolerated (Frye et al. 2000). Four trials which tested the efficacy and safety of topiramate (target doses: 200, 400 or 600 mg/day) vs. placebo (two trials included lithium, 1,500 mg/day as an active comparator) in hospitalized BD-I acutely manic or mixed patients were negative concerning the YMRS score change at week 3 vs. placebo (−5.1 vs. −8.4), while lithium was related to a significant change vs. placebo and vs. topiramate. The same finding occurred at week 12. The most frequent adverse effects related to topiramate were paraesthesia, appetite decrease, dry mouth and weight loss. Topiramate was not associated with mood destabilization measured as mania exacerbation or treatment-emergent depression (Kushner et al. 2006).

Thus, the data concerning the efficacy of lamotrigine, gabapentin, topiramate, eslicarbazepine and licarbazepine against acute mania are negative. This suggests that there is no class effect concerning antiepileptics in the treatment of BD (Fountoulakis et al. 2011a; Rosa et al. 2011).

16.2.1.1.3 Antipsychotics

Antipsychotics were developed for the treatment of psychosis, and probably the first patients on whom they were used were manic–depressive in an excited state. However, eventually their primary indication was schizophrenia and related psychotic disorders. It is well known that there is a general efficacy–effectiveness gap, and only recently there were hard data available concerning their efficacy in BP. The first study was a small, placebo-controlled study supporting the efficacy of chlorpromazine (Klein 1967). Another one took place in 1975, and it utilized a problematic methodology especially concerning the psychometric scales; it compared lithium, haloperidol and chlorpromazine and suggested that antipsychotics acted more rapidly, but lithium was more globally effective (Shopsin et al. 1975).

Haloperidol

The efficacy and safety of haloperidol was studied in five RCTs and all were positive. All of them were of 12-week duration with the first 3 weeks as a double-blind placebo-controlled phase and the next 9 weeks as the extension phase without placebo. The primary outcome was positioned at week 3. The first one was an international multicentre study of 302 hospitalized patients with acute mania and compared haloperidol (up to 8 mg/day; $N=99$) vs. quetiapine IR (flexibly dosed up to 800 mg/day; $N=102$) and placebo ($N=101$). It showed that at week 3, haloperidol- and quetiapine IR-treated patients manifested significantly more reduction in the YMRS scores (−15.71 vs. −12.29 vs. −8.32; $p<0.01$), and this was evident as early as day 4. Quetiapine IR improved all individual items of the YMRS, while no such data are reported concerning haloperidol. Although both agents reduced the PANSS positive score at endpoint, only haloperidol had an effect at week 21, and only haloperidol differed from placebo concerning the reduction of YMRS score in psychotic patients, and this was true throughout the study. On the contrary, haloperidol had a favourable effect on the MADRS at week 3 which did not last until the end of the study in contrast to quetiapine which had a sustained effect. The response rate at day 21 was in favour of the haloperidol and quetiapine IR groups in comparison to placebo (56.1 % vs. 42.6 % vs. 35.0 %). Remission rates were not significant for either drug vs. placebo at day 21, but they were at week 12 (63.3 % vs. 61.4 % vs. 38.0 %). More patients under haloperidol withdrew from the study because of adverse events in comparison to quetiapine IR and placebo (10.1 % vs. 4.9 % vs. 5.9 %). The only frequent adverse events related to haloperidol treatment were EPS which occurred more often with haloperidol than with quetiapine IR or placebo (59.6 % vs. 12.7 % vs. 15.8 %) (McIntyre et al. 2005). Another international (outside the USA) 12-week multicentre trial in 438 hospitalized acutely manic BD patients (mixed and rapid cycling excluded) compared haloperidol (2–12 mg/day; $N=144$) vs. risperidone (1–6 mg/day; $N=154$) vs. placebo ($N=140$). At week 3 both agents exhibited higher change in YMRS scores (−13.9 vs. −15.1 vs. −9.4; $p<0.001$). The effect persisted throughout the study duration, and there were no differences between the two active drug arms. There was no difference between patients with vs. without psychotic features. Response rate at week 3 was also superior for the two active drugs vs. placebo (47 % vs. 48 % vs. 33 %). Response was stable during the whole study

duration. Risperidone manifested a significant change also in the MADRS score at week 3 and at endpoint while haloperidol did only at endpoint. However in those patients who completed the study, the effect of haloperidol on the MADRS was larger than that of risperidone. EPS were more frequent in the haloperidol arm (40 % vs. 17 % vs. 9 %) at week 3, and a similar picture persisted throughout the study. There were similar rates of dropouts in the three arms at week 3 (10 % vs. 11 % vs. 15 %). Discontinuation because of adverse events was similar across arms (≤5 %), while there was some difference in the dropouts because of insufficient response (1 % vs. 3 % vs. 6 %) (Smulevich et al. 2005). The next study was again international and multicentre, included 485 acutely manic or mixed patients and assessed the efficacy and safety of aripiprazole (15 or 30 mg/day; $N=167$) vs. haloperidol (5–15 mg/day; $N=165$) vs. placebo ($N=153$). At week 3 both haloperidol and aripiprazole manifested significantly higher change in YMRS scores in comparison to placebo (−12.8 vs. −12.0 vs. −9.7; $p<0.01$), and this was maintained through week 12. Both medication arms significantly improved the positive but not the negative subscale of the PANSS. The response rates at week 3 were numerically greater with haloperidol and aripiprazole in comparison to placebo, but neither was significant (49.7 % vs. 47.0 % vs. 38.2 %; $p>0.05$). This was true also for the remission rates (45.3 % vs. 44 % vs. 36.8 %; $p>0.05$). The dropout rate was similar across the study arms at week 3 (27 % vs. 25 % vs. 29 %). Extrapyramidal adverse events were more frequent with haloperidol than aripiprazole (53.3 % vs. 23.5 %), but otherwise the adverse effects profile was similar (Young et al. 2009). Next was a 12-week international RCT on 438 acutely manic or mixed BD patients which compared haloperidol (8–30 mg/day; $N=172$) vs. ziprasidone (80–160 mg/day; $N=178$) and vs. placebo ($N=88$). At week 3, haloperidol produced greater change in MRS score in comparison to ziprasidone, but both arms did significantly better than placebo (−15.93 vs. −10.41 vs. −6.10; $p\leq0.01$). The positive subscale of the PANSS but not the other subscales was also significantly improved by the active drugs. At week 3, the response rate was significantly superior for haloperidol vs. both ziprasidone and placebo (54.7 % vs. 36.9 % vs. 20.5 %, respectively, $p<0.05$). Response was maintained until the end of the study (week 12) for both agents. At week 12, 31.9 % of haloperidol-treated patients were in remission vs. 22.7 % in the ziprasidone arm. Significantly more patients in the placebo group dropped out (59 % vs. 55 % vs. 72 %), and this was also true because of lack of efficacy (27 % vs. 12 % vs. 44 %) but not because of adverse events (9 % vs. 21 % vs. 5 %). More patients under haloperidol dropped out in comparison to patients under ziprasidone during the extension phase (weeks 4–12; 21.1 % vs. 9.6 %) and also had significantly higher rates of movement disorders as adverse events. At week 3, haloperidol-treated patients experienced more often adverse events in comparison to ziprasidone-treated patients and placebo (80.1 % vs. 64.6 % vs. 39.8 %). Throughout the study period more patients under haloperidol experienced adverse events in comparison to ziprasidone (87.1 % vs. 73.6 %). Through week 3, more patients under haloperidol had discontinued because of adverse events in comparison to ziprasidone and placebo (21 % vs. 9 % vs. 5 %) and at week 12 (21.1 % vs. 9.6 %). There was no significant difference in the cardiovascular adverse events between

the three treatment arms and in the rate of switching to depression although numerically more patients under haloperidol switched during the entire 12-week duration of the study in comparison to ziprasidone (8.7 % vs. 4.5 %). This study was powered to detect weight gain since patients included should had had body weight ≥80 % of the lower weight limit and within 150 % of the upper weight limit of the ideal weight for sex, height and frame. It is interesting that there was a big difference in body weight between countries (Vieta et al. 2010c). Finally, a 3-week study from Japan randomized 224 manic or mixed BD patients to receive haloperidol (2.5–10 mg/day; $N=20$), olanzapine (5–20 mg/day; $N=105$) or placebo ($N=99$). The haloperidol arm included only 20 patients. At week 3 the haloperidol-treated patients had significant reduction in their YMRS score in comparison to placebo and similar to olanzapine (−14.3 vs. −12.6 vs. −6.8). Olanzapine had an effect on the core symptoms of mania, while a similar effect was not present for haloperidol. The response rates were similar in the three groups (65 % vs. 51 % vs. 44.3 %), while the remission rate was higher (but not significantly) in the haloperidol group (65 % vs. 47.1 % vs. 41.2 %). Haloperidol numerically increased the HAM-D score in, while olanzapine significantly decreased it in comparison to both haloperidol and placebo. More patients under haloperidol dropped out (60 % vs. 30.5 % vs. 45.5 %), fewer because of lack of efficacy (5 % vs. 14.3 % vs. 28.9 %) but more because of adverse events (25 % vs. 8.6 % vs. 7 %). More haloperidol-treated patients switched to symptomatic depression in comparison to olanzapine (16.7 % vs. 2.4 %, $p=0.014$). The adverse events rate related with haloperidol treatment were somnolence, EPS, weight gain and constipation. EPS in the haloperidol group were more severe than in the olanzapine group (Katagiri et al. 2012).

Overall, with five positive studies (McIntyre et al. 2005; Smulevich et al. 2005; Young et al. 2009; Vieta et al. 2010c; Katagiri et al. 2012), the data are strong in favour of haloperidol (up to 30 mg/day) in the treatment of acute mania with an NNT roughly equal to 5–8 for response, which is present already since day 4. There is signal for the induction of depression in the short term. One study reported no effect on the core symptoms of mania; however, it does have an effect on psychotic symptoms. It might be particularly efficacious in psychotic patients, but its effect on mixed patients is unknown. The adverse events rate related with haloperidol treatment were somnolence, EPS, weight gain and constipation.

Olanzapine

A multicentre US 3-week duration RCT on 139 acutely manic or mixed patients (half of them psychotic) from academic centres investigated the efficacy and safety of olanzapine (up to 10 mg/day; $N=70$) vs. placebo ($N=69$). The olanzapine group experienced significantly greater mean improvement in YMRS vs. the placebo group at week 3 (−10.26 vs. −4.88, $p=0.02$), and most of the improvement was observed already since week 1. However the analysis of separate YMRS items showed that only sleep and irritability differed between arms. There was also a significant effect of olanzapine on the positive subscale of the PANSS but not on the negative subscale. Olanzapine was equally effective in patients with and without psychotic features, mixed features and rapid cycling. There was no significant effect

on the HAM-D. More patients in the olanzapine group responded in comparison to placebo (48.6 % vs. 24.2 %). More patients under placebo dropped out (65.2 % vs. 38.6 %) and also more dropped out because of lack of efficacy (47.8 % vs. 28.6 %). There was no difference in the dropout rate because of adverse effects. Somnolence, dizziness, dry mouth and weight gain but not EPS occurred significantly more often in the olanzapine-treated patients (Tohen et al. 1999). A multicentre 4-week RCT conducted in university-affiliated sites in the USA included 115 acutely manic or mixed patients (half of them psychotic) and studied the efficacy and safety of olanzapine (5–20 mg/day; $N=55$) vs. placebo ($N=60$). At week 4, olanzapine-treated patients had significantly greater reduction in the YMRS score (−14.78 vs. −8.13, $p<0.001$). This difference was evident since week 1. There was also a significant reduction in the PANSS positive subscale but not in the PANSS negative or the HAM-D. Olanzapine-treated patients demonstrated a higher rate of response (65 % vs. 43 %, $p=0.02$) than placebo-treated patients. Numerically fewer patients in the olanzapine arm dropped out (38.2 % vs. 58.3 %). Numerically more patients under olanzapine dropped out because of adverse effects (3.6 % vs. 1.7 %) and less because of lack of efficacy (27.3 % vs. 38.3 %). EPS were similar between arms; however, patients in the olanzapine arm manifested more weight gain and somnolence (Tohen et al. 2000). One study investigated the efficacy and safety of intramuscular olanzapine (10 mg, first two injections; 5 mg, third injection) vs. lorazepam (2 mg, first two injections; 1 mg, third injection) or placebo (placebo, first two injections; olanzapine, 10 mg, third injection) within a 24-h period in 201 agitated manic patients. At 2 h after the first injection, olanzapine-treated patients experienced a significantly greater reduction in agitation in comparison both to placebo and lorazepam, and the difference persisted throughout the study duration. On the contrary, lorazepam did not differ from placebo. There was no difference between groups concerning the adverse events rate, including EPS or QTc interval changes (Meehan et al. 2001). Another international multicentre study in 521 acutely manic or mixed patients evaluated the efficacy and safety of olanzapine (5–20 mg/day; $N=215$) vs. divalproex (500–2,500 mg/day; $N=201$) vs. placebo ($N=105$). At week 3, olanzapine but not divalproex-treated patients had significantly more reduction in their YMRS scores in comparison to the placebo arm (−9.4 vs. −8.2 vs. −7.4). The response rates did not differ between the medication arms and placebo (40.8 % vs. 40.3 % vs. 31.3 %) and neither did the remission rates (42.8 % vs. 40.3 % vs. 35.4 %). There was no difference in the MADRS score change between the medication arms and placebo. The dropout rate was not different between groups (26 % vs. 24.9 % vs. 26.6 %). Weight gain and somnolence were the most frequent adverse events associated with olanzapine treatment. It is interesting that while 35.4 % (at 3 weeks) to 57.1 % (at 12 weeks) had valproate plasma concentrations lower than the recommended valproate therapeutic range, the YMRS scores of these patients were lower than those of patients with valproate concentrations above or within range (Tohen et al. 2008b). Another international multicentre 3-week study in 488 acutely manic or mixed patients (rapid cycling excluded) compared olanzapine (5–20 mg/day; $N=190$) vs. asenapine (10–20 mg/day; $N=194$) vs. placebo ($N=104$). At day 21 both olanzapine and asenapine had superior changes from

baseline in the YMRS scores (−12.6 vs. −10.8 vs. −5.5, $p<0.001$), and the change was evident since day 2. Olanzapine but not asenapine significantly improved the MADRS score in comparison to placebo. This improvement was evident since day 7. Olanzapine but not asenapine improved mixed patients also. More patients under olanzapine and asenapine responded in comparison to placebo (50 % vs. 42.3 % vs. 25.2 %, $p<0.01$). The picture was similar concerning the remission rates. The dropout rate was similar in the three treatment arms (30.9 % vs. 37.1 % vs. 38.5 %); however, fewer patients dropped out because of lack of efficacy in the olanzapine group (5.8 % vs. 8.2 % vs. 16.3 %). Also the fewer patients under olanzapine dropped out because of adverse events in comparison to asenapine and similar to placebo (4.2 % vs. 10.3 % vs. 6.7 %). EPS were reported in numerically more olanzapine- and asenapine-treated patients in comparison to placebo (7.9 % vs. 7.2 % vs. 2.9 %). The most frequent adverse effects of olanzapine included sedation, dry mouth, dizziness, somnolence and weight gain (McIntyre et al. 2009a). Another international multicentre RCT of 3-week duration included 488 acutely manic or mixed BD patients (rapid cycling excluded) and studied the efficacy and safety of olanzapine (5–20 mg/day; $N=205$) vs. asenapine (10–20 mg/day; $N=185$) vs. placebo ($N=98$). Olanzapine and asenapine were superior to placebo at day 21 (−14.6 vs. −11.5 vs. −7.8, $p<0.01$). For both medication arms the treatment effect was significant since day 2. Olanzapine but not asenapine significantly improved the MADRS score at endpoint. The response rate of olanzapine, but not of asenapine, was superior to that of placebo (54.7 % vs. 42.6 % vs. 34 %). This was true also for remission rates. The dropout rate was lower in the olanzapine arm (21.5 % vs. 33 % vs. 41.8 %). Fewer patients in the olanzapine arm discontinued because of lack of efficacy (6.3 % vs. 7.6 % vs. 14.3 %) or adverse events (3.4 % vs. 9.2 % vs. 4.1 %). Most frequent adverse events related with olanzapine treatment were somnolence, dizziness, sedation and EPS. More EPS in comparison to placebo were registered in the olanzapine group but lower in comparison to asenapine (6.8 % vs. 10.3 % vs. 3.1 %). Weight gain was significantly more frequent in the olanzapine arm (19.0 % vs. 7.2 % vs. 1.2 %) (McIntyre et al. 2010b). Finally, a 3-week study from Japan randomized 224 manic or mixed BD patients to receive haloperidol (2.5–10 mg/day; $N=20$), olanzapine (5–20 mg/day; $N=105$) or placebo ($N=99$). The haloperidol arm included only 20 patients. At week 3 the haloperidol-treated patients had significant reduction in their YMRS score in comparison to placebo and similar to olanzapine (−14.3 vs. −12.6 vs. −6.8). Olanzapine had an effect on the core symptoms of mania, while a similar effect was not present for haloperidol. The response rates were similar in the three groups (65 % vs. 51 % vs. 44.3 %), while the remission rate was higher (but not significantly) in the haloperidol group (47.1 % vs. 65 % vs. 41.2 %). Haloperidol numerically increased the HAM-D score, while olanzapine significantly decreased it in comparison to both haloperidol and placebo. More patients under haloperidol dropped out (60 % vs. 30.5 % vs. 45.5 %), fewer because of lack of efficacy (5 % vs. 14.3 % vs. 28.9 %) but more because of adverse events (25 % vs. 8.6 % vs. 7 %). More haloperidol-treated patients switched to symptomatic depression in comparison to olanzapine (16.7 % vs. 2.4 %, $p=0.014$). The adverse events related with olanzapine treatment were somnolence, dizziness,

thirst and weight gain. EPS in olanzapine group were less severe than in the haloperidol group (Katagiri et al. 2012). The efficacy and safety of olanzapine has also been investigated in a study sample of 45 outpatients (24 BD-1, 22 BD-II and 4 BD-NOS) with HAM-D ≥10 and/or YMRS ≥10 and ≤24. This diverse group of patients was randomized to double-blind olanzapine (2.5–20 mg/day; $N=23$) vs. placebo ($N=22$) for 1 week. At endpoint, olanzapine did not differ from placebo in any outcome; however, there were trends towards a superiority of olanzapine, and the study was underpowered. On the other hand there was a significant weight gain and more EPS in the olanzapine group (Srivastava et al. 2012).

Taken together the above, the literature supports the efficacy of olanzapine 5–20 mg/day for the treatment of manic or mixed episodes and concomitant psychotic features. There are six positive trials supporting this efficacy (Tohen et al. 1999, 2000, 2008b; McIntyre et al. 2009a, 2010b; Katagiri et al. 2012). The NNT is approximately around 5 for response. Although the results are not satisfactorily consistent, olanzapine seems to have a beneficial effect on the core symptoms of mania, on psychotic symptoms, and treats mixed patients as well as rapid cycling, and the response is visible as early as days 2–7. Olanzapine does not seem to switch to depression and possibly improves the coexisting depressive symptoms. The adverse events related with olanzapine treatment were somnolence, dizziness, dry mouth, thirst and weight gain. There was also a low rate of EPS.

Quetiapine

An international multicentre 12-week RCT (3 weeks with placebo) in 302 acutely manic patients compared quetiapine IR (flexibly dosed up to 800 mg/day; $N=107$) vs. lithium (target serum levels 0.6–1.4 mEq/l; $N=98$) and vs. placebo ($N=97$). The improvement in YMRS score was significantly greater for quetiapine IR, and lithium in comparison to placebo at day 21 (−14.6 vs. −15.2 vs.−6.7; $p<0.001$) was present already during day 7 and persisted throughout the duration of the study. Significantly more quetiapine IR- and lithium-treated patients were responders in comparison with placebo patients at day 21 (53.3 % vs. 53.1 % vs. 27.4 %; $p<0.001$), and the picture was similar concerning the remission rates (46.7 % vs. 49 % vs. 22.1 %; $p<0.001$). The picture was similar concerning remission rates. Quetiapine IR improved all individual YMRS items, but the respected data for lithium were not reported. Quetiapine IR but not lithium significantly improved the PANSS positive subscale, and both improved the activation and the aggression subscale. The effect on the negative subscale was not reported. Both medications significantly improved the MADRS score, but quetiapine IR achieved this already at day 21 while lithium only at endpoint. Fewer patients in the quetiapine IR and lithium groups dropped out from the study compared with the placebo group (32.7 % vs. 31.6 % vs. 63.9 %). Also fewer of them dropped out because of lack of efficacy (14.9 % vs. 12.2 % vs. 39.2 %), while the dropout rate because of adverse events was similar among groups (6.5 % vs. 6.1 % vs. 4.1 %). The most common adverse events for quetiapine IR were dry mouth, somnolence, and weight gain. The quetiapine IR and placebo groups had similar, low levels of EPS (Bowden et al. 2005b). Another international multicentre study of 302 hospitalized BD patients with acute mania compared

quetiapine IR (flexibly dosed up to 800 mg/day; $N=102$) vs. haloperidol (up to 8 mg/day; $N=99$) and placebo ($N=101$). It showed that at week 3, quetiapine IR- and haloperidol-treated patients manifested significantly more reduction in the YMRS scores (−12.29 vs. −15.71 vs. −8.32; $p<0.01$), and this was evident as early as day 4. Quetiapine IR improved all individual items of the YMRS, while no such data are reported concerning haloperidol. Although both agents reduced the PANSS positive score at endpoint, quetiapine had no effect at week 21 and did not differ from placebo concerning the reduction of YMRS score in psychotic patients, and this was true throughout the study. On the contrary, quetiapine IR had a sustained effect on the MADRS which started as early as week 3, while haloperidol had a favourable effect at week 3 which however did not last until the end of the study. The response rate at day 21 was in favour of the quetiapine IR and haloperidol groups in comparison to placebo (42.6 % vs. 56.1 % vs. 35.0 %). Remission rates were not significant for either drug vs. placebo at day 21, but they were at week 12 (61.4 % vs. 63.3 % vs. 38.0 %). Quetiapine IR had less frequent EPS in comparison to haloperidol and similar to placebo (12.7 % vs. 59.6 % vs. 15.8 %). Also fewer patients under quetiapine IR withdrew from the study because of adverse events in comparison to haloperidol and similar to placebo (4.9 % vs. 10.1 % vs. 5.9 %). The only frequent adverse events related to quetiapine were somnolence and postural hypotension (McIntyre et al. 2005). The NCT00309699 was an international multicentre 12-week (3 weeks with placebo) study which included 493 acutely manic or mixed patients and compared quetiapine IR (400–800 mg/day; $N=193$) vs. paliperidone ER (3–12 mg/day; $N=195$), vs. placebo ($N=105$). Both quetiapine IR and paliperidone ER significantly improved the YMRS at week 3 in comparison to placebo (−11.7 vs. −13.2 vs. −7.4; $p<0.001$). The treatment effect was evident as early as day 2 and lasted for the entire duration of the study, and it was similar for manic and mixed patients. Although a beneficial effect on total PANSS score was reported, no specific effects on the positive or negative subscales of the PANSS or on a depressive scale were included in the report. At week 3 more patients in the two treatment arms were responders in comparison to placebo (49 % vs. 55.8 % vs. 34.6 %). Similarly the remission rate was higher in both treatment arms in comparison to placebo at week 3 (47.4 % vs. 52.1 % vs. 28.8 %). This picture lasted for the entire duration of the study, and a similar picture was observed concerning the remission rates. The NNT for response or remission was 6–7 for quetiapine IR. At week 3 fewer patients under quetiapine IR or paliperidone ER dropped out in comparison to placebo (21.2 % vs. 20.5 % vs. 39 %). Fewer patients in the medication arms withdrew because of lack of efficacy in comparison to placebo, and these withdrawals were more in the quetiapine IR group in comparison to the paliperidone ER group (7.8 % vs. 3.1 % vs. 18.1 %). Dropout because of adverse events was similar in the three arms. The most common treatment-emergent adverse events related to quetiapine were somnolence, sedation, dry mouth, headache and dizziness. At week 12 the body weight increase was more frequent in the quetiapine IR group (17 % vs. 8 %), but more patients under paliperidone ER switched to depression (13.9 % vs. 7.5 %) (Vieta et al. 2010b). Another one, the NCT00422123, which was a US multicentre 3-week RCT, included 308 acutely manic or mixed BD patients and

compared quetiapine XR (400–800 mg/day, $N=149$) with placebo ($N=159$). At week 3 quetiapine IR improved the YMRS in comparison to placebo (−14.3 vs. −10.5; $p<0.001$). The treatment effect was evident as early as day 4 and lasted for the entire duration of the study, and it was significant for manic but not for mixed or rapid cycling patients. Quetiapine XR improved 6 out of 11 YMRS items, including core items. There was also a beneficial effect on the MADRS score as early as day 4 for manic patients alone. No effect on psychotic symptoms was reported. At week 3 more patients in quetiapine XR arm were responders in comparison to placebo (55.0 % vs. 33.3 %). This picture lasted for the entire duration of the study, and a similar picture was observed concerning the remission rates. The NNT for response or remission was 6–7 for quetiapine IR. The dropout rate was similar in the two groups (29.1 % vs. 28.1 %). Fewer patients in the medication arm withdrew because of lack of efficacy in comparison to placebo (3.9 % vs. 9.4 %). The dropout because of adverse events was higher in the placebo group. The adverse events associated with quetiapine XR treatment were mild to moderate in intensity and included sedation, dry mouth and somnolence (Cutler et al. 2011). Finally a small 8-week RCT in two US sites in 41 bipolar spectrum disorder patients and moderate-to-severe hypomanic or mild manic symptoms (hypomania/mild mania) studied quetiapine IR (up to 800 mg/day; $N=21$) vs. placebo ($N=20$). Quetiapine IR-treated patients had a marginally but nonsignificant improvement in YMRS score in comparison to placebo ($p=0.06$). Some secondary outcomes were significant. Discontinuation rates were high and similar in the two groups (McElroy et al. 2010b).

Taken together the above, with four positive studies (Bowden et al. 2005b; McIntyre et al. 2005; Vieta et al. 2010b; Cutler et al. 2011), the literature supports the efficacy of quetiapine up to 800 mg/day for the treatment of acute mania. There is some doubt concerning its efficacy against mixed episodes and concomitant psychotic features, while it is not efficacious in rapid cycling patients. The NNT is approximately 2–6 for response. Quetiapine does not seem to switch to depression, and on the contrary there is a clear beneficial effect on concomitant depressive symptoms. The adverse events associated with quetiapine treatment included sedation, dry mouth, somnolence, headache, dizziness and postural hypotension.

Aripiprazole

Aripiprazole was studied in four studies. The first one was a 3-week multicentre US study in 262 acutely manic or mixed BD patients and tested aripiprazole (15–30 mg/day; $N=130$) vs. placebo ($N=132$). Aripiprazole significantly improved the YMRS score at week 3 in comparison to placebo (−8.2 vs. −3.4; $p=0.002$) and produced a significantly higher response rate (40 % vs. 19 %; $p<0.005$). Improvement was evident as early as day 4. This study did not report on the effect on psychotic and depressive symptoms. Fewer patients under aripiprazole dropped out (58 % vs. 79 %). Dropout due to adverse events or lack of efficacy was similar between groups. The most frequent aripiprazole-related adverse events were nausea, dyspepsia, somnolence, anxiety, vomiting, insomnia, light-headedness, constipation and akathisia. There were no significant changes in body weight, serum prolactin or QTc prolongation (Keck et al. 2003a). Another 3-week multicentre US study in 272

hospitalized acutely manic or mixed BD patients compared aripiprazole (15–30 mg/day; $N=137$), with placebo ($N=135$). Aripiprazole significantly improved the YMRS score at week 3 in comparison to placebo (−12.5 vs. −7.2; $p<0.001$), and this was evident as early as day 4. It also produced a significantly higher response rate (53 % vs. 32 %; $p<0.001$) which was present already at day 7. Aripiprazole produced significant change in the PANSS positive and hostility subscales but not in the PANSS negative subscale or the MADRS. The therapeutic effect was evident also in the rapid cycling and mixed patients subgroups. In the latter group, a significant effect on the MADRS was also present. Dropout rate was similar in the two groups (55 % vs. 52 %) and was also similar due to adverse events but due to lack of efficacy was double in the placebo group (9 % vs. 21 %). It was similar for aripiprazole (8.8 %) and placebo (7.5 %). Aripiprazole treatment resulted in no significant difference from placebo in change in mean body weight and was not associated with elevated serum prolactin or QTc prolongation. The most common adverse events with aripiprazole were nausea, somnolence, akathisia, dyspepsia, extremity pain and constipation (Sachs et al. 2006). Another one was a 12-week multicentre US study in 480 acutely manic or mixed patients (rapid cycling excluded) which investigated aripiprazole (15–30 mg/day; $N=155$) vs. lithium (900–1,500 mg/day; $N=160$) vs. placebo ($N=165$). Both aripiprazole and lithium demonstrated significantly greater improvement than placebo in YMRS score at week 3 (−12.6 vs. −12.0 vs. −9.0; $p<0.005$), and the improvement was evident since day 2 for aripiprazole and since week 1 for lithium and continued during all the study period. The response rate was significantly higher in both the aripiprazole and lithium groups in comparison to placebo at week 3 (46.8 % vs. 45.8 % vs. 34.4 %; $p<0.05$). A similar picture was concerning remission rates (40.3 % vs. 40 % vs. 28.2 %). Aripiprazole improved the PANSS cognitive and hostility subscales at week 3, but no effect on PANSS was observed for lithium. No results concerning the PANSS positive and negative subscales were reported. Neither agent had any effect on the MADRS scores. The dropout rate was similar between groups (53 % vs. 51 % vs. 53 %) at week 3. Fewer patients in the aripiprazole group dropped out because of lack of efficacy (6 % vs. 16 % vs. 22 %), while more patients in the two medication arms dropped out because of adverse events in comparison to placebo (15 % vs. 13 % vs. 8 %). The most common adverse events with aripiprazole were headache, nausea, akathisia, sedation and constipation (Keck et al. 2009). The next study was again international and multicentre, included 485 acutely manic or mixed patients and assessed the efficacy and safety of aripiprazole (15 or 30 mg/day; $N=167$) vs. haloperidol (5–15 mg/day; $N=165$) vs. placebo ($N=153$). At week 3 both aripiprazole and haloperidol manifested significantly higher change in YMRS scores in comparison to placebo (−12.0 vs. −12.8 vs. −9.7; $p<0.01$), and this was maintained through week 12. Both medication arms significantly improved the positive but not the negative subscale of the PANSS. The response rates at week 3 were numerically greater with haloperidol and aripiprazole in comparison to placebo, but neither was significant (47.0 % vs. 49.7 % vs. 38.2 %; $p>0.05$). This was true also for the remission rates (44 % vs. 45.3 % vs. 36.8 %; $p>0.05$). The dropout rate was similar across the study arms at week 3 (25 % vs. 27 % vs. 29 %). Extrapyramidal adverse events were less frequent

with aripiprazole in comparison to haloperidol (23.5 % vs. 53.3 %), but otherwise the adverse effects profile was similar (Young et al. 2009). Finally, one international 3-week RCT on 401 hospitalized acutely manic or mixed BD patients evaluated the efficacy and safety of two fixed doses of aripiprazole (15 mg/day, $N=131$ and 30 mg/day, $N=136$) vs. placebo ($N=134$). Neither aripiprazole arm was better than placebo in any of the outcomes (YMRS, MADRS, PANSS total and hostility subscale and response rates), and overall withdrawal rates were similar also. Interestingly, the placebo response was generally higher than expected. The most frequent adverse events for either of the aripiprazole treatment groups were headache, nausea, dyspepsia, insomnia, agitation, constipation, akathisia, anxiety, lightheadedness, vomiting, diarrhoea, asthenia and extremity pain (El Mallakh et al. 2010). One study has not been completed and reported no results (A Multicentre, Randomized, Double-Blind, Placebo-Controlled Study of Aripiprazole in the Treatment of Acutely Manic Patients with Bipolar Disorder (Protocol CN138077)).

Taken together the above, with three positive (Keck et al. 2003a, 2009; Sachs et al. 2006) and one negative fixed dosage study (El Mallakh et al. 2010), the literature supports the efficacy of aripiprazole 15–30 mg/day for the treatment of acute manic and mixed episodes. The effect on the core symptoms of mania is unknown. There is a significant effect in mixed and rapid cycling patients, and it also treats concomitant positive psychotic features and agitation but not negative symptoms. It does not seem to have any effect on depressive symptoms. The NNT is approximately around 5–10 for response. Aripiprazole does not seem to switch to depression. Nausea, dyspepsia, somnolence, anxiety, vomiting, insomnia, light-headedness, constipation and akathisia were the most common adverse events. There were no significant effects on body weight, serum prolactin or QTc prolongation.

Risperidone

Another 3-week multicentre US study included 259 acutely manic BD patients (mixed excluded) and assessed the efficacy and safety of risperidone (1–6 mg/day; $N=134$) vs. placebo ($N=125$). Risperidone-treated patients manifested a significant change in the YMRS scores in comparison to placebo (−10.6 vs. −4.8; $p<0.001$), and the effect was evident since day 3. More patients under risperidone responded at week 3 (43 % vs. 24 %). The improvements in the MADRS score and four of the five PANSS factors (positive symptoms, disorganized thoughts, uncontrolled hostility/excitement and anxiety/depression) were also significant. The results were similar in patients with and without psychotic features. The most common risperidone-related adverse events were somnolence, dyspepsia, nausea and EPS (Hirschfeld et al. 2004). A second 3-week multicentre study from India included 290 acutely manic or mixed hospitalized BD patients (rapid cycling excluded) that assessed the efficacy and safety of risperidone (1–6 mg /day; $N=146$) vs. placebo ($N=144$). Risperidone-treated patients manifested significantly more change in the YMRS at week 3 (−23.2 vs. −10.8, $p<0.001$), and the improvement was evident since week 1. More patients under risperidone were responders at week 3 (73 % vs. 36 %; $p<0.001$). There was a significant effect also on the MADRS scores and the PANSS positive symptoms and uncontrolled excitement/hostility factors but not on

the other PANSS subscales. The therapeutic effect was similar in manic vs. mixed and psychotic vs. nonpsychotic patients. Fewer patients under risperidone dropped out (10.9 % vs. 28.9 %). The dropout rate was similar because of adverse events, while fewer patients under risperidone dropped out because of lack of efficacy (4.8 % vs. 14.5 %). EPS were the most frequently reported adverse events in the risperidone group (Khanna et al. 2005). This study sparked a debate concerning the limits of the use of placebo in similar studies (Mudur 2006; Patel 2006). Another international (outside the USA) 12-week multicentre trial in 438 hospitalized acutely manic patients (mixed and rapid cycling excluded) compared risperidone (1–6 mg/day; $N=154$) vs. haloperidol (2–12 mg/day; $N=144$) vs. placebo ($N=140$). At week 3 both agents exhibited higher change in YMRS scores (−15.1 vs. −13.9 vs. −9.4; $p<0.001$). The effect persisted throughout the study duration, and there were no differences between the two active drug arms. There was no difference between patients with vs. without psychotic features. Response rate at week 3 was also superior for the two active drugs vs. placebo (48 % vs. 47 % vs. 33 %). Response was stable during the whole study duration. Risperidone manifested a significant change also in the MADRS score at week 3 and at endpoint, while haloperidol did only at endpoint. However in those patients who completed the study, the effect of haloperidol on the MADRS was larger than that of risperidone. EPS were more frequent in the haloperidol arm (17 % vs. 40 % vs. 9 %) at week 3, and a similar picture persisted throughout the study. There were similar rates of dropouts in the three arms at week 3 (11 % vs. 10 % vs. 15 %). Discontinuation because of adverse events was similar across arms (≤5 %), while there was some difference in the dropouts because of insufficient response (3 % vs. 1 % vs. 6 %) (Smulevich et al. 2005).

Thus, the literature with four positive studies (Gopal et al. 2005; Hirschfeld et al. 2004; Khanna et al. 2005; Smulevich et al. 2005) supports the efficacy of risperidone 1–6 mg/day for the treatment of acute manic and mixed episodes, which is evident since day 3. It seems also effective in the treatment of positive psychotic features and agitation and concomitant depressive but not negative symptoms. The NNT is approximately around 3–5 for response. It is unknown whether risperidone has an effect on the core symptoms of mania or whether it is beneficial for rapid cycling patients. It does not seem to switch to depression. Somnolence, dyspepsia, nausea and EPS were the most common adverse events.

Ziprasidone

An international (USA and Brazil) 3-week multicentre RCT in 210 acutely manic or mixed patients assessed the efficacy and safety of ziprasidone (80–160 mg/day; $N=140$) or placebo ($N=70$). At week 3, ziprasidone-treated patients achieved more reduction in the MRS score in comparison to placebo (12.4 vs. 7.8; $p<0.005$). The improvement was evident already since day 2, concerned also the core symptoms of mania and was similar in manic and mixed patients. There was a beneficial effect of ziprasidone on total PANSS score, but no effect on the subscales is reported. Significantly more patients under ziprasidone were responders (50 % vs. 35 %; $p<0.05$). Fewer patients under ziprasidone dropped out (46.4 % vs. 55.7 %), and this was also true because of lack of efficacy (19.3 % vs. 35.7 %) but not because of

adverse events (3.6 % vs. 1.4 %). Ziprasidone was related to a low rate of EPS. There was no weight gain observed. The most frequent adverse events were somnolence, dizziness, akathisia and hypertonia (Keck et al. 2003b). Another 3-week international (USA, Brazil and Mexico) RCT included 206 acutely manic or mixed BD patients and studied the efficacy and safety of ziprasidone (80–160 mg/day; $N=140$) vs. placebo ($N=66$). Ziprasidone-treated patients manifested significantly greater reduction in the MRS scores at week 3 (−11.1 vs. −5.6; $p<0.01$). The improvement concerned also the core symptoms of mania and was evident as early as day 2. The responder rate at study endpoint was significantly higher in the ziprasidone group (46 % vs. 29 %; $p<0.05$). A significant improvement was also evident concerning the positive but not the negative subscale of the PANSS. There was an early improvement of HAM-D and MADRS scores; however, at endpoint ziprasidone did not differ from placebo. The discontinuation rate was similar in the two arms (39.3 % vs. 45.5 %). Fewer patients under ziprasidone dropped out because of lack of efficacy (12.9 % vs. 28.8 %) but more because of adverse events (5.7 % vs. 1.5 %). Ziprasidone treatment was related with EPS, somnolence and dizziness (Potkin et al. 2005). The next was a 12-week international RCT on 438 acutely manic or mixed BD patients which compared ziprasidone (80–160 mg/day; $N=178$) vs. haloperidol (8–30 mg/day; $N=172$) and vs. placebo ($N=88$). At week 3, ziprasidone produced smaller change in MRS score in comparison to haloperidol, but both arms did significantly better than placebo (−10.41 vs. −15.93 vs. −6.10, $p<0.01$), and the change concerned the core manic symptoms and was significant since day 2. Both medication arms improved the positive but not the negative subscale of the PANSS. There was no significant effect of either medication on the HAM-D or the MADRS. At week 3, the response rate was significantly superior for haloperidol vs. both ziprasidone and placebo (36.9 % vs. 54.7 % vs. 20.5 %; $p<0.05$). Response was maintained until the end of the study (week 12) for both agents. At week 12, 31.9 % of haloperidol-treated patients were in remission vs. 22.7 % in the ziprasidone arm. Significantly more patients in the placebo group dropped out (59 % vs. 55 % vs. 72 %), and this was also true because of lack of efficacy (27 % vs. 12 % vs. 44 %) but not because of adverse events (9 % vs. 21 % vs. 5 %). The adverse events related with ziprasidone treatment were EPS, akathisia, somnolence, dystonia/hypotonia, dizziness, tremor, anxiety and dyspepsia. There was no significant difference in the cardiovascular adverse events between the three treatment arms and in the rate of switching to depression although numerically more patients under haloperidol switched during the entire 12-week duration of the study in comparison to ziprasidone (8.7 % vs. 4.5 %). This study was powered to detect weight gain since patients included should had had body weight ≥80 % of the lower weight limit and within 150 % of the upper weight limit of the ideal weight for sex, height and frame. It is interesting that there was a big difference in body weight between countries (Vieta et al. 2010c).

Taken together the above, on the basis of three positive studies (Keck et al. 2003b; Potkin et al. 2005; Vieta et al. 2010c), the literature supports the efficacy of ziprasidone 80–160 mg/day for the treatment of acute manic and mixed episodes. It has a treatment effect on the core symptoms of mania, but the effect in rapid cycling

patients is unknown. It is effective in the treatment of concomitant positive psychotic features but not negative symptoms. It does not seem to have any significant effect on depressive symptoms. The NNT is approximately 6 for response. Ziprasidone does not seem to switch to depression. The adverse events related with ziprasidone treatment were EPS, somnolence, dizziness, anxiety and dyspepsia. There were no significant effects on body weight or serum lipids. There was a small QTc prolongation.

Asenapine

Concerning asenapine, the first international multicentre RCT of 3-week duration (Ares 7501004; NCT00159744) included 488 acutely manic or mixed patients (rapid cycling excluded) and studied the efficacy and safety of asenapine (10–20 mg/day; $N=185$) vs. olanzapine (5–20 mg/day; $N=205$) vs. placebo ($N=98$). Asenapine and olanzapine were superior to placebo at day 21 (−11.5 vs. −14.6 vs. −7.8, $p<0.01$). For both medication arms the treatment effect was significant since day 2. Asenapine did not improve significantly the MADRS score at endpoint; however, olanzapine did. The response rate of asenapine was not superior to that of placebo, while that of olanzapine was 42.6 % vs. 54.7 % vs. 34 %. This was true also for remission rates. The dropout rate was lower in the olanzapine arm (33 % vs. 21.5 % vs. 41.8 %). Fewer patients in the treatment arms discontinued because of lack of efficacy (7.6 % vs. 6.3 % vs. 14.3 %) or adverse events (9.2 % vs. 3.4 % vs. 4.1 %). Most frequent adverse events related with asenapine treatment were somnolence, dizziness, sedation and EPS. The asenapine group experienced more EPS in comparison to placebo and to the olanzapine group (10.3 % vs. 6.8 % vs. 3.1 %). Weight gain was significantly more frequent in both treatment arms in comparison to placebo, but it was more pronounced in the olanzapine arm (19.0 % vs. 7.2 % vs. 1.2 %) (McIntyre et al. 2010b). The second was a 3-week duration (Ares 7501005; NCT00159796) in 488 BD patient suffering from an acute manic or mixed episode (rapid cycling excluded) and investigated the efficacy and safety of asenapine (10–20 mg/day; $N=194$) vs. olanzapine (5–20 mg/day; $N=190$) vs. placebo ($N=104$). At day 21 both asenapine and olanzapine had superior changes from baseline in the YMRS scores (−10.8 vs. −12.6 vs. −5.5, $p<0.001$), and the change was evident since day 2. Olanzapine but not asenapine improved mixed patients also. Asenapine did not improve the MADRS score in comparison to placebo; however, olanzapine did. More patients under asenapine and olanzapine responded in comparison to placebo (42.3 % vs. 50 %vs. 25.2 %, $p<0.01$). The picture was similar concerning the remission rates. The dropout rate was similar in the three treatment arms (37.1 % vs. 30.9 % vs. 38.5 %); however, fewer patients dropped out because of lack of efficacy in the asenapine group in comparison to placebo (8.2 % vs. 5.8 % vs. 16.3 %). However more patients under asenapine dropped out because of adverse events in comparison to olanzapine and placebo (10.3 % vs. 4.2 % vs. 6.7 %). EPS were reported in numerically more asenapine- and olanzapine-treated patients in comparison to placebo (7.2 % vs. 7.9 % vs. 2.9 %). The most frequent adverse effects of asenapine included sedation, dizziness, somnolence, fatigue, oral hypaesthesia, dry mouth, EPS and weight gain (McIntyre et al. 2009a).

Thus, on the basis of two positive trials (McIntyre et al. 2009a, 2010b), the literature supports the efficacy of asenapine 10–20 mg/day for the treatment of acute manic and mixed episodes and is effective as early as day 2. It is not reported whether it has a treatment effect on the core symptoms of mania, and the effect in rapid cycling patients is unknown. It is unknown whether it is effective in the treatment of concomitant positive or negative psychotic features, and it does not seem to have any significant effect on depressive symptoms. The NNT is between 6 and 12 for response. Asenapine does not seem to switch to depression. The adverse events related with asenapine treatment were EPS, somnolence, dizziness, sedation, fatigue, oral hypaesthesia, dry mouth, weight gain and EPS.

Paliperidone

Paliperidone was studied in two RCTs. The NCT00309699 was an international multicentre 12-week study which included 493 acutely manic or mixed patients and compared paliperidone ER (3–12 mg/day; $N=195$) vs. quetiapine IR (400–800 mg/day; $N=193$) vs. placebo ($N=105$). Both paliperidone ER and quetiapine IR significantly improved the YMRS at week 3 in comparison to placebo (−13.2 vs. −11.7 vs. −7.4; $p<0.001$). The treatment effect was evident as early as day 2 and lasted for the entire duration of the study, and it was similar for manic and mixed patients. Although a beneficial effect on total PANSS score was reported, no specific effects on the positive or negative subscales of the PANSS or on a depressive scale were included in the report. At week 3 more patients in the two treatment arms were responders in comparison to placebo (55.8 % vs. 49 % vs. 34.6 %). Similarly the remission rate was higher in both treatment arms in comparison to placebo at week 3 (52.1 % vs. 47.4 % vs. 28.8 %). This picture lasted for the entire duration of the study, and a similar picture was observed concerning the remission rates. The NNT for response or remission was 5 for paliperidone ER. At week 3 fewer patients under paliperidone ER or quetiapine IR dropped out in comparison to placebo (20.5 % vs. 21.2 % vs. 39 %). Fewer patients in the medication arms withdrew because of lack of efficacy in comparison to placebo, and these withdrawals were more in the quetiapine IR group in comparison to the paliperidone ER group (3.1 % vs. 7.8 % vs. 18.1 %). Dropout because of adverse events were similar in the three arms. The most common treatment-emergent adverse events were headache, somnolence and akathisia for paliperidone ER. At week 12 the body weight increase was more frequent in the quetiapine IR group (17 % vs. 8 %), but more patients under paliperidone ER switched to depression (13.9 % vs. 7.5 %) (Vieta et al. 2010b). The second paliperidone ER study was an international 3-week RCT in 469 BD patients in an acute manic or mixed episode and investigated the efficacy and safety of three fixed doses of once-daily paliperidone ER (3 mg/day; $N=112$, 6 mg/day; $N=120$, or 12 mg/day; $N=115$) or placebo ($n=122$). At week 3 the chance in YMRS was different in comparison to placebo only in the ER 12 mg group (−13.5 vs. −10.1; $p=0.025$), but not in the 6 mg or 3 mg groups compared with placebo. There was no effect on the MADRS or PANSS total score, and paliperidone ER did not shift patients to depression. There was no difference between any medication arm and placebo concerning response and remission rates. It was not reported

whether the 12 mg dosage had an effect on the core manic symptoms. The dropout rate was similar in the 12 mg group and placebo (34.8 % vs. 41 %). Fewer patients in the 12 mg group dropped out because of lack of efficacy (6 % vs. 19.7 %) but more because of adverse events (7.8 % vs. 4.9 %) in comparison to placebo. Headache, EPS and prolactin elevation were the most common treatment-emergent adverse events. It is interesting to note that a significant treatment-by-country interaction occurred, which confounded interpretation of study results. There was no response observed in patients from the US sites (74 % of study sample), while on the contrary such an effect was observed in the rest countries. The efficacy for the overall study population was driven largely, but not exclusively, by patients from India (Berwaerts et al. 2012b).

These two studies (Vieta et al. 2010b; Berwaerts et al. 2012b) provide some support for the efficacy of paliperidone ER 3–12 mg/day for the treatment of acute manic and mixed episodes and is effective as early as day 2. It is not reported whether it has a treatment effect on the core symptoms of mania, positive psychotic symptoms and depression, and the effect in rapid cycling patients is unknown. The NNT is approximately around 5 for response. It is unclear whether paliperidone ER switches to depression. The adverse events related with paliperidone ER treatment were headache, somnolence and EPS, and prolactin elevation was the most common treatment-emergent adverse event.

Cariprazine

Three unpublished studies (NCT00488618, NCT01058096 and NCT01058668) confirmed the efficacy of cariprazine vs. placebo in the treatment of acute mania. The NCT00488618 was an international multicentre randomized, double-blind, placebo-controlled study which tested cariprazine (3–12 mg/day; $N=118$) vs. placebo ($N=120$) in acutely manic or mixed type, with or without psychotic features BD patients (rapid cycling excluded). The results suggested that cariprazine significantly reduced YMRS score at week 3 compared to placebo. The effect was present in all YMRS items separately. Cariprazine also improved the total PANSS but had no effect on the MADRS. More patients under cariprazine were responders (48 % vs. 25 %), and this was the picture concerning remission also. The most common adverse events were EPS, headache, constipation, nausea and dyspepsia. The NCT01058096 was an international multicentre randomized, double-blind, placebo-controlled study which tested cariprazine (3–12 mg/day; $N=158$) vs. placebo ($N=154$) in acutely manic or mixed type, with or without psychotic features BD patients (rapid cycling excluded), and suggested that cariprazine was superior to placebo already since day 4. Cariprazine also improved the total PANSS but had no effect on the MADRS. More patients under cariprazine were responders (59 % vs. 44 %), and this was the picture concerning remission also. The adverse effect profile included EPS but not weight gain, metabolic disturbances, prolactin increase or QTc prolongation. The dropout rate because of adverse events was similar with placebo (10 % vs. 7 %). The results of the NCT01058668 which tested cariprazine 3–6 mg/day ($N=167$) and 6–12 mg/day ($N=169$) vs. placebo ($N=161$) have not

been fully publicized yet. However that study included acutely manic or mixed type, with or without psychotic features BD patients, and there was a statistically significant improvement in both cariprazine dose groups vs. placebo on the YMRS scores. The most common adverse events were akathisia (both cariprazine groups) and constipation (for the cariprazine 6–12 mg/day group). Discontinuations due to adverse events were similar (9 % in the 3–6 mg/day group; 15 % in the 6–12 mg/day group and 5 % in the placebo group) (Altinbas et al. 2013; Citrome 2013).

Overall these data support the efficacy of cariprazine against acute manic or mixed episodes. The NNT for response or remission is approximately 4–6. Cariprazine is reported to improve the core symptoms of mania but had no effect on the MADRS. It improves the total PANSS, but the specific effect on the PANSS positive subscale is unknown. Its efficacy in mixed and rapid cycling patients is unknown.

16.2.1.1.4 Other Agents and Treatment Modalities

Tamoxifen

A small pilot 3-week study on 16 manic or mixed patients with or without psychotic features subjects (treatment-naïve patients excluded) investigated the efficacy and safety of tamoxifen (20–140 mg/day; $N=8$) vs. placebo ($N=8$) for 3 weeks. Tamoxifen-treated patients showed significant improvement in the YMRS in comparison to placebo (−18.3 vs. +4.7) already since day 5, an effect that remained significant throughout the 3-week trial. Tamoxifen had a significant effect on the core symptoms of mania, and the overall effect size was very large ($d=1.08$; $p=0.001$). There was no significant effect on PANSS and MADRS scores. At study endpoint, response rates were 63 % for tamoxifen and 13 % for placebo. The small study sample precluded the detection of a significant outcome concerning response and remission rates; however, the study supported the notion that further research on tamoxifen was important. The most common adverse event related with tamoxifen was loss of appetite (Zarate et al. 2007). Two trials followed: An NIMH-sponsored clinical trial (NCT00026585) has not reported results yet, while a second one came from Turkey and was sponsored by the Stanley Medical Research Institute (NCT00411203). This was 3 weeks small in 66 manic or mixed patients with or without psychotic features which investigated the efficacy and safety of tamoxifen (40–160 mg/day; $N=35$) vs. placebo ($N=31$). At week 3 tamoxifen significantly reduced the YMRS score in comparison to placebo (−5.84 vs. +1.5; $p<0.01$) and had an effect in the core symptoms of mania. It also reduced significantly the PANSS positive and general psychopathology subscales but not the negative PANSS subscale or the MADRS. There was a superiority also concerning the response rate (48 % vs. 5 %; $p<0.002$) and a similar picture concerning the remission rate. Fewer patients under tamoxifen dropped out because of worsening (17 % vs. 32 %). The adverse events reported in the tamoxifen group were headache, worsening of acne, dry skin, urticaria, flushing and loss of appetite (Yildiz et al. 2008). Overall, the data for tamoxifen are positive; however, the total patient sample is still small.

Verapamil
One small 3-week study on 32 acutely manic patients investigated the efficacy and safety of verapamil ($N=17$) vs. placebo ($N=15$). The results suggested no benefit of verapamil over placebo in treating acute mania (Janicak et al. 1998).

Electroconvulsive Therapy (ECT)
There are no RCTs testing the efficacy and safety of monotherapy ECT vs. a placebo condition in acutely manic or mixed BD patients.

Transcranial Magnetic Stimulation (rTMS)
The data concerning rTMS are conflicting. There are two RCTs testing the efficacy and safety of rTMS vs. a placebo condition in acutely manic BD patients. The first utilized a right vs. sham prefrontal TMS of 20 Hz, 2-s duration per train, 20 trains per day for 10 treatment days, in 25 acutely manic patients. The results suggested there was no difference between treatment groups (Kaptsan et al. 2003). The second examined the efficacy of adjunctive right prefrontal high-frequency suprathreshold rTMS (20 Hz, 110 % of MT, 20 trains, 10 s intertrain interval for 10 days) vs. sham stimulation in 41 right-handed acutely manic patients. At endpoint there was a significant effect of treatment over time (Praharaj et al. 2009).

16.2.1.1.5 Summary of Monotherapy Trials for Acute Mania

Overall there are sufficient data in the literature to support the general efficacy of a number of agents in the treatment of acute mania; however, many details remain to be explored concerning many of the agents. Lithium, valproate, carbamazepine, haloperidol, olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone, asenapine, paliperidone, cariprazine and probably tamoxifen are efficacious in the treatment of acute manic episodes. It is sad that there are no controlled data concerning the usefulness of ECT and rTMS.

A significant problem for the everyday clinical practice is that the average clinician often utilizes the so-called 'class effect' in order to easily navigate among therapeutic options. However, what needs to be stressed is that while antipsychotics seem to possess a 'class effect' restricted to the treatment of acute mania (possibly an antidopaminergic effect) (Brugue and Vieta 2007), there is no such an effect in anticonvulsants concerning any phase of BD (Fountoulakis et al. 2011a; Rosa et al. 2011).

16.2.1.2 Comparison of Agents

16.2.1.2.1 Lithium Versus Others

Lithium was used as the standard in order to compare the efficacy and safety of newer compounds. Therefore there is a wealth of data comparing it with other agents.

It has been compared with valproate in two studies. The first was a 3-week study in 27 manic patients that compared lithium (at serum levels 1.5 mmol/l) vs. valproate (1,500–3,000 mg/day). The response rate was higher in the lithium arm (92.3 % vs. 64.3 %). The favourable response to valproate was associated with high

pretreatment depression scores, thus implying that treatment with valproate alone may be particularly efficacious in manic patients with mixed affective states (Freeman et al. 1992). The second was a 3-week study in 179 hospitalized, acutely manic patients in academic settings across the USA, which tested the efficacy and safety of lithium (serum levels below 1.5 mmol/l; $N=36$) vs. divalproex (serum levels below 150 μg/ml; $N=69$) and vs. placebo ($N=74$). Half of patients were previously nonresponsive to lithium, and none had previously received valproate; thus, the study sample was enriched in favour of divalproex. After 3 weeks, both treatment arms manifested a higher change in MRS in comparison to placebo, and this change was significant since day 15 for both agents. Unfortunately the results are reported only through a chart, and no exact means and standard deviations are available. Interestingly, the analysis of separate items of the MRS revealed that divalproex but not lithium had a beneficial effect on the core manic symptoms. The response rate was higher for lithium and divalproex in comparison to placebo (49 % vs. 48 % vs. 25 %; $p=0.025$). In spite of the fact that half of patients were previously unresponsive to lithium, no inferiority of lithium in comparison to divalproex was observed. Fewer patients in the divalproex arm dropped out (61 % vs. 48 % vs. 64 %). Dropouts because of lack of efficacy were fewer in the two treatment arms in comparison to placebo (33 % vs. 30 % vs. 51 %), while dropouts because of adverse events were more frequent with lithium (11 % vs. 6 % vs. 3 %). The most frequent adverse events with lithium were asthenia, constipation, dizziness, nausea, fever, twitching and vomiting, while with divalproex were asthenia, constipation, dizziness, nausea, twitching and vomiting (Bowden et al. 1994).

Lithium was compared with carbamazepine in three studies. The first one was a small 4-week study on 34 manic patients testing carbamazepine vs. lithium reported that the two treatment arms were similar in terms of efficacy. The dropout rate was similar too (17.6 %). There was a signal suggesting that while lithium was effective in a homogenous way in the total sample of patients which were included in the lithium arm, carbamazepine had a beneficial effect only in a minority of patients in the carbamazepine-treated group. The findings suggest that carbamazepine has antimanic potential in specific bipolar patients whose clinical characteristics remain to be clearly defined (Lerer et al. 1987). The second was a multicentre 4-week study from Japan in 105 patients (of which 80 % were also receiving antipsychotics and were somewhat refractory to them at dosages equivalent to 8 mg of haloperidol) with bipolar disorders. It compared carbamazepine ($N=51$) vs. lithium ($N=54$) both at 400–1,200 mg/day and showed that both agents had similar response rates (moderate to marked amelioration of manic symptoms in 62 and 59 %, respectively). Carbamazepine had a somewhat earlier onset of actin, but both agents needed at least 2 weeks for the majority of the responders to manifest the response. However the mean lithium serum levels were below the recommended therapeutic range (0.46 ± 0.22 mEq/l). The dropout rate was similar (15.7 % vs. 22.2 %), but more patients in the carbamazepine group dropped out because of adverse events while more in the lithium group because of lack of efficacy. The incidence of adverse events was higher in the carbamazepine group (60 % vs. 43 %). The main adverse events encountered in patients receiving carbamazepine were drowsiness,

unsteadiness, lassitude, dizziness, weakness, thirst, constipation and cutaneous symptoms, while in the patients receiving lithium, they were unsteadiness, thirst, drowsiness, lassitude, dizziness, anorexia and polyuria. The incidence of cutaneous symptoms (exanthema) was significantly higher in the carbamazepine group (12 % vs. 0 %) (Okuma et al. 1990). The third study was on 52 hospitalized and rather refractory to treatment of manic patients, which were randomized to carbamazepine vs. lithium carbonate for 8 weeks, and reported that one-third were responders without any difference between arms (Small et al. 1991).

One small 4-week pilot study in 30 manic inpatients compared lamotrigine (25 mg once daily for 1 week, 50 mg once daily for the second week and 100 mg once daily for the last 2 weeks) vs. lithium (800 mg/day). Of course it should be noted that monotherapy data for lamotrigine in acute mania are clearly negative. There were no significant differences between groups at any time point, suggesting that the dose escalation required for lamotrigine did not adversely affect its onset of action. However both agents were probably administered at a too low dosage. Secondary outcome measures, including the use of lorazepam as rescue medication, did not differ between the groups. No significant adverse events were noted in either group. However since lamotrigine has negative placebo-controlled RCTs, this should be considered to be a failed study (Ichim et al. 2000).

Three studies compared lithium with chlorpromazine. The first study was small, included 23 manic patients and tested lithium carbonate ($N=13$) vs. chlorpromazine ($N=10$). It reported that lithium carbonate was superior to chlorpromazine on all six parameters selected from an objective rating scale (Platman 1970). The second one was a multicentre trial which included 18 hospitals and 255 newly admitted manic patients. It tested lithium carbonate vs. chlorpromazine for 3 weeks. Patients were classified as highly active or mildly active on the basis of degree of motor activity shown at admission. Chlorpromazine acted earlier and was superior to lithium in the more agitated patients, but lithium overall produced a better subjective mental state in patients. Chlorpromazine had fewer dropouts and had a lower incidence of severe side effects, but lithium had a lower incidence of overall side effects (Prien et al. 1972). Finally, a 3-week comparison, in 30 severely ill hospitalized manic patients, tested lithium carbonate (up to blood levels of 2.0 mEq/l; $N=10$) vs. haloperidol (up to 26 mg/day; $N=10$) vs. chlorpromazine (up to 2,500 mg/day; $N=10$). The results suggested the three agents were equal, although the scales used were not satisfactorily sensitive. Lithium produced a highly significant improvement of manic symptoms without sedation, while chlorpromazine produced considerable sedation but had little effect on the core manic symptoms per se. More patients under lithium remitted and met discharge criteria at study termination (Shopsin et al. 1975).

Another two studies compared lithium with haloperidol. In a 3-week comparison, 30 severely ill hospitalized manic patients were administered with lithium carbonate (up to blood levels of 2.0 mEq/l; $N=10$), haloperidol (up to 26 mg/day; $N=10$) or chlorpromazine (up to 2,500 mg/day; $N=10$). The results suggested the three agents were equal, although the scales used were not satisfactorily sensitive. Lithium and haloperidol produced a highly significant improvement of manic symptoms without sedation, while chlorpromazine produced considerable sedation but

had little effect on the core manic symptoms per se. The comparison of haloperidol and lithium revealed some qualitative differences with haloperidol having a more rapid effect especially on behaviour and motor activity, while lithium acted more evenly and completely on the entire manic symptomatology. More patients under lithium remitted and met discharge criteria at study termination (Shopsin et al. 1975). The second was again a 3-week study in 21 severely ill manic inpatients and investigated the comparative efficacy of lithium (up to 900 mg/day; $N=7$) vs. haloperidol (up to 30 mg/day; $N=7$) vs. a combination of haloperidol–lithium ($N=7$). Subjects on haloperidol and the haloperidol–lithium combination were significantly improved after 7 days in comparison to the lithium-treated group. The haloperidol and the haloperidol–lithium combination groups did not differ from each other, either in degree of improvement or in side effects and were superior to lithium monotherapy (Garfinkel et al. 1980).

Lithium was compared with olanzapine in three studies. In the first, which was a small one, 30 acutely manic patients were randomly allocated to receive either olanzapine (10 mg/day; $N=15$) or lithium (800 mg/day; $N=15$) in a 4-week double-blind randomized controlled design. There were no significant differences between the two groups on any of the primary outcome measures and especially in the mania scale (10.2 vs. 13.2; $p=0.315$). There was no difference between arms concerning EPS (Berk et al. 1999). Another multicentre 4-week study in 140 acutely manic or mixed patients from China examined the efficacy and safety of olanzapine (5–20 mg/day, $N=69$) vs. lithium carbonate (600–1,800 mg/day, $N=71$). A significantly greater mean change was observed in the olanzapine arm concerning the YMRS score (−24.63 vs. −20.15; $p=0.013$). Both arms showed a significant reduction in the MADRS score, which did not differ between arms. More patients under olanzapine responded (87 % vs. 73.2 %; $p=0.035$), while the remission rate was similar in the two arms (82.6 % vs. 70.4 %; $p=0.073$). However 32.8 % of the lithium-treated patients did not achieve the target serum levels. Fewer (though not significantly) patients under olanzapine dropped out (8.7 % vs. 21.1 %; $p=0.07$), but more patients experienced at least one adverse event (36.2 % vs. 19.7 %; $p=0.038$). The most common adverse events related to olanzapine were weight gain, constipation, nausea, somnolence, nasopharyngitis, vomiting, diarrhoea, dizziness and restlessness, while those related with lithium were nausea and nasopharyngitis. More patients under olanzapine manifested a clinically significant weight increase (16.2 % vs. 2.9 %; $p=0.009$) (Niufan et al. 2008). A 3-week study from Iran included 40 female acutely manic inpatients (mixed excluded) and studied the efficacy and safety of olanzapine (20.52 ± 4.37 mg/day; $N=20$) vs. lithium ($1{,}156 \pm 249.32$ mg/day and serum level 0.78 ± 0.269 mEq/l; $N=20$). At the end of the trial, although lithium performed better than olanzapine in terms of the mania scale used, more patients under olanzapine manifested at least 50 % improvement (25 % vs. 15 %). The main reported side effects of olanzapine were weight gain, tremor and sedation, while for lithium it was tremor (Shafti 2010).

There are two studies comparing lithium with quetiapine. An international multicentre 12-week RCT (3 weeks with placebo) in 302 acutely manic BD patients compared lithium (target serum levels 0.6–1.4 mEq/l; $N=98$) vs. quetiapine IR

(flexibly dosed up to 800 mg/day; $N=107$) and vs. placebo ($N=97$). The improvement in YMRS score was significantly greater for lithium, and quetiapine IR in comparison to placebo at week 3 (−15.2 vs. −14.6 vs. −6.7; $p<0.001$) was present already during day 7 and persisted throughout the duration of the study. Significantly more lithium- and quetiapine IR-treated patients were responders in comparison with placebo patients at week 3 (53.1 % vs. 53.3 % vs. 27.4 %; $p<0.001$), and the picture was similar concerning the remission rates (49 % vs. 46.7 % vs. 22.1 %; $p<0.001$). While the quetiapine IR data concerning all individual YMRS items were reported, this was not done also for lithium. Quetiapine IR but not lithium significantly improved the PANSS positive subscale, and both improved the activation and the aggression subscale. The effect on the negative subscale was not reported. Both medications significantly improved the MADRS score, but lithium achieved this only at endpoint, while quetiapine IR already at day 21. Fewer patients in the lithium and quetiapine IR groups dropped out from the study compared with the placebo group (31.6 % vs. 32.7 % vs. 63.9 %). Also fewer of them dropped out because of lack of efficacy (12.2 % vs. 14.9 % vs. 39.2 %), while the dropout rate because of adverse events was similar among groups (6.1 % vs. 6.5 % vs. 4.1 %). The most common adverse events for lithium were tremor and insomnia, while for quetiapine they were dry mouth, somnolence and weight gain (Bowden et al. 2005b). The second study came from China and was a 4-week multicentre study in 154 manic patients (mixed excluded, more than 70 % without psychotic symptoms) that compared quetiapine (up to 800 mg/day; $N=77$) vs. lithium (up to 2,000 mg/day with target serum concentration 0.6–1.2 mmol/l; $N=77$). At week 4, a significant change in the YMRS scores was present in both treatment arms (−18.2 vs. −15.9). A similar significant change was present concerning the MADRS and the total PANSS scores also. The response rate was higher in the quetiapine group (77.9 % vs. 59.7 %; $p=0.01$), and a similar picture was present concerning the remission rates (70.1 % vs. 48.1 %; $p<0.01$). More patients under lithium dropped out (5.2 % vs. 19.5 %). For two consecutive visits, 20.8 % of lithium-treated patients had serum levels below 0.6 mmol/l. More patients under quetiapine experienced at least one adverse event (78.2 % vs. 68.8 %). The most common adverse events experienced by the quetiapine-treated group were constipation, dizziness, diarrhoea, alanine aminotransferase increase, palpitations, aspartate aminotransferase increase, pharyngolaryngeal pain, upper respiratory tract infection and dry mouth, while in the lithium-treated patients, they were nausea, constipation, vomiting, nasopharyngitis, dizziness, diarrhoea and upper respiratory tract infection. The proportion of patients with weight gain of >70 % at week 4 was higher in the quetiapine group (9.9 % vs. 6.5 %) (Li et al. 2008).

Finally, it has also been compared to aripiprazole in a 12-week (3 weeks with placebo) multicentre US study in 480 acutely manic or mixed patients (rapid cycling excluded). The study investigated lithium (900–1,500 mg/day; $N=160$) vs. aripiprazole (15–30 mg/day; $N=155$) vs. placebo ($N=165$). Both lithium and aripiprazole demonstrated significantly greater improvement than placebo in YMRS score at week 3 (−12.0 vs. −12.6 vs. −9.0; $p<0.005$), and the improvement was evident since week 1 for lithium and since day 2 for aripiprazole and continued for all the

study period. The response rate was significantly higher in both the lithium and the aripiprazole groups in comparison to placebo at week 3 (45.8 % vs. 46.8 % vs. 34.4 %; $p<0.05$). A similar picture was evident concerning the remission rates (40 % vs. 40.3 % vs. 28.2 %). No effect on PANSS total or MADRS was observed for lithium. No results concerning the PANSS positive and negative subscales were reported. The dropout rate was similar between groups (51 % vs. 53 % vs. 53 %) at week 3. The dropout rate for lithium because of lack of efficacy was between that of aripiprazole and placebo (16 % vs. 6 % vs. 22 %), while more patients in the two medication arms dropped out because of adverse events in comparison to placebo (13 % vs. 15 % vs. 8 %). The most common adverse events with lithium were nausea, headache, constipation and tremor while with aripiprazole were headache, nausea, akathisia, sedation and constipation (Keck et al. 2009).

Conclusively, lithium was found superior or non-inferior to valproate (Freeman et al. 1992; Bowden et al. 1994) and equal to carbamazepine (Lerer et al. 1987; Okuma et al. 1990; Small et al. 1991), olanzapine (Berk et al. 1999; Niufan et al. 2008; Shafti 2010), quetiapine (Bowden et al. 2005b; Li et al. 2008) and aripiprazole (Keck et al. 2009), but inferior to haloperidol (Shopsin et al. 1975; Garfinkel et al. 1980). Overall lithium manifested a wider antimanic effect than valproate and carbamazepine but without an effect on psychotic symptoms and with slower onset of action in comparison to antipsychotics. Overall it manifested a more favourable adverse effect profile in comparison to all other agents except aripiprazole and valproate.

16.2.1.2.2 Valproate Versus Others

Valproate has also been used as kind of a standard for comparison with newer agents. Thus there is a significant number of studies involving it.

It has been compared to lithium in two studies (Freeman et al. 1992; Bowden et al. 1994). Both are discussed above in the 'lithium' section.

There is only one study comparing valproate with carbamazepine. That study came from India and was conducted in 30 manic inpatients (24 of them females; valproate $N=15$; carbamazepine $N=15$). It reported that the valproate group showed a significant fall in YMRS total scores already after week 1, while the carbamazepine group showed a significant fall only after week 2. At endpoint the difference was significant in favour of valproate (−32.8 vs. −20.8; $p=0.02$). The valproate group demonstrated a numerically greater mean improvement relative to the carbamazepine group on all YMRS items except sleep. More patients under valproate responded (73 % vs. 53 %). Only three patients in each group dropped out. Serum levels for carbamazepine did not correlate with clinical response, while on the contrary the levels of valproate correlated with clinical response. Significantly more patients in the carbamazepine group reported adverse events, including nausea, vomiting and dizziness, than valproate (17 % vs. 67 %) (Vasudev et al. 2000).

Another three papers compared valproate to olanzapine. One randomized, 12-week multicentre study included 120 patients hospitalized for acute mania or mixed episode and randomly assigned them to treatment with divalproex (750–3,250 mg/day; $N=63$) vs. olanzapine (5–25 mg/day; $N=57$). No significant differences between groups were found concerning the change in MRS scores from

baseline to week 3 (−14.8 vs. −17.2; $p=0.210$). The two treatment arms produced similar changes in the BPRS and the HAM-D as well. The effect on psychotic symptoms was unclear. At week 3 numerically more patients under divalproex dropped out (38 % vs. 32 %). Similarly, numerically more patients under divalproex dropped out because of adverse events (11 % vs. 9 %) and because of lack of efficacy (22 % vs. 19 %) at the end of the study. More olanzapine-treated subjects experienced somnolence, weight gain, oedema, rhinitis and speech disorder (slurred speech), while no adverse events were significantly greater in the divalproex group (Zajecka et al. 2002). The second was a 3-week study in 148 hospitalized manic or mixed patients (approximately half of them mixed and half of them rapid cycling) that compared olanzapine (5–20 mg/day; $N=125$) vs. divalproex (500–2,500 mg/day in divided doses; targeted therapeutic range 50–125 μg/ml; $N=123$) and reported that there was a greater decrease in the YMRS score for the olanzapine group (−13.4 vs. −10.4; $p=0.03$), and the difference was present already at day 2. There was also a superiority concerning the response (54.4 % vs. 42.3 %; $p=0.06$) and remission rates (47.2 % vs. 34.1 %; $p=0.04$) which were also achieved faster in the olanzapine group. The change in the HAM-D was similar in the two treatment groups. In the subgroup without psychotic features, olanzapine was superior to divalproex, while in the psychotic group the two arms were equal. Also the overall dropout rate was similar (31.2 % vs. 35.7 %) also concerning because of adverse events (9.6 % vs. 7.1 %) and lack of efficacy (8.8 % vs. 9.5 %). The most common treatment-emergent adverse events related to olanzapine were dry mouth, increased appetite and somnolence, while for divalproex, nausea was more frequently observed. The average weight gain with olanzapine treatment was 2.5 kg, compared to 0.9 kg with divalproex treatment (Tohen et al. 2002a). Finally, an international multicentre study in 521 acutely manic or mixed patients evaluated the efficacy and safety of olanzapine (5–20 mg/day; $N=215$) vs. divalproex (500–2,500 mg/day; $N=201$) vs. placebo ($N=105$). At week 3, olanzapine- but not divalproex-treated patients had significantly more reduction in their YMRS scores in comparison to the placebo arm (−9.4 vs. −8.2 vs. −7.4). The response rates did not differ between the medication arms and placebo (40.8 % vs. 40.3 % vs. 31.3 %) and neither did the remission rates (42.8 % vs. 40.3 % vs. 35.4 %). There was no difference in the MADRS score change between the medications arms and placebo. The dropout rate was not different between groups (26 % vs. 24.9 % vs. 26.6 %). Weight gain and somnolence were the most frequent adverse events associated with olanzapine treatment. It is interesting that while 35.4 % (at 3 weeks) to 57.1 % (at 12 weeks) had valproate plasma concentrations lower than the recommended valproate therapeutic range, the YMRS scores of these patients were lower than those of patients with valproate concentrations above or within range (Tohen et al. 2008b).

One 12-week study from India in 60 patients with acute mania (mixed and rapid cycling excluded) assessed divalproex (750–2,000 mg/day; $N=30$) vs. oxcarbazepine (1,000–2,400 mg/day; $N=30$). At endpoint, the improvement in YMRS scores was comparable, and the remission rates were also similar (90 % vs. 80 %). A significantly greater number of patients in the divalproex group experienced one or more adverse events (66.7 % vs. 30 %, $p<0.01$). The most frequent adverse events

related to divalproex were nausea, dizziness, vomiting, headache, pain in abdomen, sedation, weight gain, dyspepsia, increased appetite and constipations, while those related with oxcarbazepine were nausea, dizziness, vomiting, headache, sedation and dyspepsia (Kakkar et al. 2009).

Conclusively, in comparison to lithium, valproate was less efficacious and with a tendency to manifest fewer adverse events and dropouts, but its efficacy might be restricted to a specific minority of patients with mixed features (Freeman et al. 1992; Bowden et al. 1994). In one small study it was superior to carbamazepine and with faster action (Vasudev et al. 2000). In another it was superior to oxcarbazepine but with more frequent adverse events (Kakkar et al. 2009). It might be less efficacious in comparison to olanzapine and with a slower onset of action (although this could be a function of dosage), but also with fewer adverse events (Tohen et al. 2002a, 2008b; Zajecka et al. 2002).

16.2.1.2.3 Carbamazepine Versus Others

There are three studies comparing carbamazepine with lithium (Lerer et al. 1987; Okuma et al. 1990; Small et al. 1991) and one with valproate (Vasudev et al. 2000). All are discussed above in the respected sections.

One study in 17 manic patients tested carbamazepine (up to 1,600 mg/day; $N=8$) vs. haloperidol (up to 80 mg/day; $N=9$). The response to carbamazepine started between days 3–7, while that to haloperidol started within the first 3 days. However after day 7 the change in YMRS score was similar in both groups (−11.9 vs. −12.0) although more patients under carbamazepine manifested remission (75 % vs. 33 %) (Brown et al. 1989).

One more small 5-week study from Japan in 60 manic (only one mixed) patients assessed the efficacy and safety of carbamazepine (up to 900 mg/day; $N=30$) vs. chlorpromazine (up to 450 mg/day; $N=30$). Although there was a trend for carbamazepine to be more efficacious, the difference was not significant. More than one-third of patients responded by week 1, and almost all who responded had done so by week 2. At least one adverse event was present in 59 % of carbamazepine and 86 % of the chlorpromazine group. The main side effects encountered in patients receiving carbamazepine were drowsiness, headache, cutaneous symptoms (exanthema), dry mouth, lassitude and dizziness, while in the chlorpromazine group they were drowsiness, headache, dizziness, dry mouth, lassitude, orthostatic hypotension, feeling of weakness, hypersalivation and nasal stuffiness. Three patients in the carbamazepine and 5 in the chlorpromazine arm dropped out; two patients from each arm dropped out because of adverse events (Okuma et al. 1979).

Conclusively, carbamazepine was reported to be equally effective in comparison to lithium and with more frequent adverse events, but its efficacy was somewhat restricted to an undefined subgroup of patients in contrast to a wider efficacy of lithium (Lerer et al. 1987; Okuma et al. 1990; Small et al. 1991). In one other study carbamazepine was inferior to valproate and with slower onset of action (Vasudev et al. 2000). In two other studies carbamazepine was found equal to chlorpromazine but with fewer adverse events (Okuma et al. 1979) and equal to haloperidol but with slower onset of action (Brown et al. 1989).

16.2.1.2.4 Other Antiepileptics

Although except valproate and carbamazepine all other antiepileptics have negative data concerning the treatment of acute mania, it is interesting to see the comparison trials they are involved. Essentially these trials might be considered as including some kind of 'active placebo'.

There is probably one failed study on lamotrigine vs. lithium (Ichim et al. 2000) and another one on oxcarbazepine vs. divalproex (Kakkar et al. 2009). Both are discussed above in the respected sections of lithium and valproate.

16.2.1.2.5 Haloperidol Versus Others

Haloperidol has served as the golden standard in trials of any kind of psychotic states for long. It has also served as the golden standard for acute mania trials no matter whether psychotic features were present or not.

There is one study comparing haloperidol with carbamazepine (Brown et al. 1989) and two with lithium (Garfinkel et al. 1980; Shopsin et al. 1975). They are both discussed above in the respected carbamazepine and lithium sections.

Two studies compared haloperidol with olanzapine. A 12-week (2 successive, 6-week, double-blind periods) international study in 453 acutely manic or mixed patients compared the efficacy and safety of olanzapine (5–20 mg/day; $N=234$) vs. haloperidol (3–15 mg/day; $N=219$). At week 6 the change in YMRS scores was greater for the haloperidol group (−23.5 vs. −21.3; $p=0.03$), but olanzapine-treated patients covered the difference by week 12 (−26.5 vs. −26.8). Rates of response and remission at week 6 were similar (55 % vs. 62 % and 52.1 % vs. 46.1 %, respectively), and time to remission was also similar (median 34 vs. 29 days). For the subgroup of patients whose index episode did not include psychotic features, rates of remission were significantly greater for the olanzapine group compared with the haloperidol group (56.7 % vs. 41.6 %, $p=0.04$). A trend towards a higher efficacy of olanzapine in the more severely ill patients was also present. The dropout rate was lower for the olanzapine group (40.2 % vs. 47 %), but it was identical because of lack of efficacy (15 % vs. 15 %) and slightly different because of adverse events (8.1 % vs. 11.4 %). Both agents were equally effective in reducing the HAM-D score in mixed patients and in patients with higher depressive scores. Relapse rates into an affective episode (mania and/or depression) was similar in both groups (13.1 % vs. 14.8 %) but switch to depression occurred significantly more rapidly with haloperidol than with olanzapine. A trend for patients under haloperidol to switch more frequently to depression was also present (9.4 % vs. 16.8 %; $p=0.1$). Significantly more haloperidol-treated patients experienced worsening of EPS and increased salivation, while somnolence, sedation, weight gain, infection, dizziness and fever were significantly greater in the olanzapine group. It is important that 5 (2.3 %) haloperidol-treated patients developed tardive dyskinesia vs. none in the olanzapine group (Tohen et al. 2003a). A 3-week study from Japan randomized 224 manic or mixed BD patients to receive haloperidol (2.5–10 mg/day; $N=20$), olanzapine (5–20 mg/day; $N=105$) or placebo ($N=99$). The haloperidol arm included only 20 patients. At week 3 the haloperidol-treated patients had significant reduction in their YMRS score in comparison to placebo and similar to olanzapine (−14.3

vs. −12.6 vs. −6.8). Olanzapine had an effect on the core symptoms of mania, while a similar effect was not present for haloperidol. The response rates were similar in the three groups (65 % vs. 51 % vs. 44.3 %), while the remission rate was higher (but not significantly) in the haloperidol group (65 % vs. 47.1 % vs. 41.2 %). Haloperidol numerically increased the HAM-D score, while olanzapine significantly decreased it in comparison to both haloperidol and placebo. More patients under haloperidol dropped out (60 % vs. 30.5 % vs. 45.5 %), fewer because of lack of efficacy (5 % vs. 14.3 % vs. 28.9 %) but more because of adverse events (25 % vs. 8.6 % vs. 7 %). More haloperidol-treated patients switched to symptomatic depression in comparison to olanzapine (16.7 % vs. 2.4 %, $p=0.014$). The adverse events rate related with haloperidol treatment were somnolence, EPS, weight gain and constipation, while those related with olanzapine treatment were somnolence, dizziness, thirst and weight gain. EPS in olanzapine group were less severe than in the haloperidol group. EPS in the haloperidol group were more severe than in the olanzapine group (Katagiri et al. 2012).

One international multicentre study of 302 hospitalized patients with acute mania and compared haloperidol (up to 8 mg/day; $N=99$) vs. quetiapine IR (flexibly dosed up to 800 mg/day; $N=102$) and placebo ($N=101$). It showed that at week 3, haloperidol- and quetiapine IR-treated patients manifested significantly more reduction in the YMRS scores (−15.71 vs. −12.29 vs. −8.32; $p<0.01$), and this was evident as early as day 4. Haloperidol was superior to quetiapine ($p<0.05$). Quetiapine IR improved all individual items of the YMRS, while no such data are reported concerning haloperidol. Although both agents reduced the PANSS positive score at endpoint, only haloperidol had an effect at week 21, and only haloperidol differed from placebo concerning the reduction of YMRS score in psychotic patients, and this was true throughout the study. On the contrary, haloperidol had a favourable effect on the MADRS at week 3 which did not last until the end of the study in contrast to quetiapine which had a sustained effect. The response rate at day 21 was in favour of the haloperidol and quetiapine IR groups in comparison to placebo (56.1 % vs. 42.6 % vs. 35.0 %). Remission rates were not significant for either drug vs. placebo at day 21, but they were at week 12 (63.3 % vs. 61.4 % vs. 38.0 %). More patients under haloperidol withdrew from the study because of adverse events in comparison both to quetiapine IR and placebo (10.1 % vs. 4.9 % vs. 5.9 %). The only frequent adverse events related to haloperidol treatment were insomnia and EPS which occurred more often with haloperidol than with quetiapine IR or placebo (59.6 % vs. 12.7 % vs. 15.8 %). Insomnia, somnolence and EPS were the most frequent adverse events related with quetiapine IR treatment (McIntyre et al. 2005).

Two studies compared haloperidol with risperidone. A 4-week study in 45 inpatients with acute mania, of risperidone (6 mg/day; $N=15$) vs. haloperidol (10 mg/day; $N=15$) vs. lithium (800–1,200 mg/daily; $N=15$), reported no differences among groups. The extrapyramidal side effects of risperidone and haloperidol were not significantly different (Segal et al. 1998). Another international (outside the USA) 12-week multicentre trial in 438 hospitalized acutely manic BD patients (mixed and rapid cycling excluded) compared haloperidol (2–12 mg/day; $N=144$) vs. risperidone (1–6 mg/day; $N=154$) vs. placebo ($N=140$). At week 3 both agents

exhibited higher change in YMRS scores (−13.9 vs. −15.1 vs. −9.4; $p<0.001$). The effect persisted throughout the study duration, and there were no differences between the two active drug arms. There was no difference between patients with vs. without psychotic features. Response rate at week 3 was also superior for the two active drugs vs. placebo (47 % vs. 48 % vs. 33 %). Response was stable during the whole study duration. Risperidone manifested a significant change also in the MADRS score at week 3 and at endpoint, while haloperidol did only at endpoint. However in those patients who completed the study, the effect of haloperidol on the MADRS was larger than that of risperidone. EPS were more frequent in the haloperidol arm (40 % vs. 17 % vs. 9 %) at week 3, and a similar picture persisted throughout the study. There were similar rates of dropouts in the three arms at week 3 (10 % vs. 11 % vs. 15 %). Discontinuation because of adverse events was similar across arms (≤5 %), while there was some difference in the dropouts because of insufficient response (1 % vs. 3 % vs. 6 %). Adverse events reported in more than 10 % of patients during the whole 12 weeks of double-blind treatment were EPS, somnolence and hyperkinesia in the risperidone group and EPS, hyperkinesia, tremor and hypertonia in the haloperidol group (Smulevich et al. 2005).

There are two studies comparing haloperidol with aripiprazole. An international 12-week multicentre study in 347 manic or mixed patients (only 11 % mixed, rapid cycling excluded) compared aripiprazole (15–30 mg/day; $N=175$) vs. haloperidol (10–15 mg/day; $N=172$). At week 12, the change in YMRS score was similar in the two treatment arms (−19.9 vs. −18.2), but significantly more patients taking aripiprazole were responders (49.7 % vs. 28.4 %; $p<0.001$) and remitters (50 % v. 27 %; $p<0.001$). Aripiprazole improved significantly more the MADRS score than haloperidol, and more haloperidol-treated patients switched to depression (11 % vs. 17.7 %; $p=0.08$). Fewer patients under aripiprazole dropped out (49.1 % vs. 70.1 %), and this was true also due to adverse events (18.3 % vs. 48.8 %) but not due to lack of efficacy (17.1 % vs. 5.8 %). In both groups the most frequent adverse events were EPS, insomnia and headache. EPS were more frequent with haloperidol than aripiprazole (24.0 % vs. 62.7 %) (Vieta et al. 2005a). The next study was again international and multicentre, included 485 acutely manic or mixed patients and assessed the efficacy and safety of aripiprazole (15 or 30 mg/day; $N=167$) vs. haloperidol (5–15 mg/day; $N=165$) vs. placebo ($N=153$). At week 3 both haloperidol and aripiprazole manifested significantly higher change in YMRS scores in comparison to placebo (−12.8 vs. −12.0 vs. −9.7; $p<0.01$), and this was maintained through week 12. Both medication arms significantly improved the positive but not the negative subscale of the PANSS. The response rates at week 3 were numerically greater with haloperidol and aripiprazole in comparison to placebo, but neither was significant (49.7 % vs. 47.0 % vs. 38.2 %; $p>0.05$). This was true also for the remission rates (45.3 % vs. 44 % vs. 36.8 %; $p>0.05$). The dropout rate was similar across the study arms at week 3 (27 % vs. 25 % vs. 29 %). Extrapyramidal adverse events were more frequent with haloperidol than aripiprazole (53.3 % vs. 23.5 %), but otherwise the adverse effects profile was similar (Young et al. 2009).

One study compared haloperidol with ziprasidone. It was a 12-week international RCT on 438 acutely manic or mixed BD patients which compared

haloperidol (8–30 mg/day; $N=172$) vs. ziprasidone (80–160 mg/day; $N=178$) and vs. placebo ($N=88$). At week 3, haloperidol produced greater change in MRS score in comparison to ziprasidone, but both arms did significantly better than placebo (−15.93 vs. −10.41 vs. −6.10; $p \leq 0.01$). The positive subscale of the PANSS but not the other subscales was also significantly improved by the active drugs. At week 3, the response rate was significantly superior for haloperidol vs. both ziprasidone and placebo (54.7 % vs. 36.9 % vs. 20.5 %, respectively; $p<0.05$). Response was maintained until the end of the study (week 12) for both agents. At week 12, 31.9 % of haloperidol-treated patients were in remission vs. 22.7 % in the ziprasidone arm. Significantly more patients in the placebo group dropped out (59 % vs. 55 % vs. 72 %), and this was also true because of lack of efficacy (27 % vs. 12 % vs. 44 %) but not because of adverse events (9 % vs. 21 % vs. 5 %). More patients under haloperidol dropped out in comparison to patients under ziprasidone during the extension phase (weeks 4–12; 21.1 % vs. 9.6 %) and also had significantly higher rates of movement disorders as adverse events. At week 3, haloperidol-treated patients experienced more often adverse events in comparison to ziprasidone-treated patients and placebo (80.1 % vs. 64.6 % vs. 39.8 %). Throughout the study period more patients under haloperidol experienced adverse events in comparison to ziprasidone (87.1 % vs. 73.6 %). Through week 3, more patients under haloperidol had discontinued because of adverse events in comparison to ziprasidone and placebo (21 % vs. 9 % vs. 5 %) and at week 12 (21.1 % vs. 9.6 %). There was no significant difference in the cardiovascular adverse events between the three treatment arms and in the rate of switching to depression although numerically more patients under haloperidol switched during the entire 12-week duration of the study in comparison to ziprasidone (8.7 % vs. 4.5 %). This study was powered to detect weight gain since patients included should had had body weight ≥80 % of the lower weight limit and within 150 % of the upper weight limit of the ideal weight for sex, height and frame. It is interesting that there was a big difference in body weight between countries (Vieta et al. 2010c).

Finally two different dosages of haloperidol were compared. That study tested 25 mg/day vs. 5 mg/day of haloperidol as add-on lithium, placebo or lorazepam for 21 days in 63 acutely psychotic bipolar manic inpatients reported that the high haloperidol dose produced greater improvement (response rate 41 % vs. 24 % at day 4; 78 % vs. 48 % at day 21) and more side effects than did the low dose but with more side effects (Chou et al. 1999).

Overall haloperidol was found comparable in efficacy with carbamazepine (Brown et al. 1989), olanzapine (Tohen et al. 2003a; Katagiri et al. 2012), quetiapine (McIntyre et al. 2005), risperidone (Segal et al. 1998; Smulevich et al. 2005) and aripiprazole (Vieta et al. 2005a; Young et al. 2009). It was found superior to lithium (Shopsin et al. 1975; Garfinkel et al. 1980) and ziprasidone (Vieta et al. 2010c). It acted faster in comparison to lithium (Shopsin et al. 1975; Garfinkel et al. 1980), carbamazepine (Brown et al. 1989) and olanzapine (Tohen et al. 2003a; Katagiri et al. 2012). Overall it manifested superior efficacy on psychotic patients but less effect (if any) on depressive symptoms. It also manifested more adverse events (especially EPS), switching to depression and dropouts than the comparison agents.

16.2.1.2.6 Olanzapine Versus Others

Three studies comparing olanzapine with lithium (Berk et al. 1999; Shafti 2010; Niufan et al. 2008), three with valproate (Zajecka et al. 2002; Tohen et al. 2002a, 2008b) and two with haloperidol (Tohen et al. 2003a; Katagiri et al. 2012) have been discussed above in the respected sections.

There are two studies comparing olanzapine with asenapine. The first was an international multicentre 3-week study in 488 acutely manic or mixed patients (rapid cycling excluded) which compared olanzapine (5–20 mg/day; $N=190$) vs. asenapine (10–20 mg/day; $N=194$) vs. placebo ($N=104$). At day 21 both olanzapine and asenapine had superior changes from baseline in the YMRS scores (−12.6 vs. −10.8 vs. −5.5, $p<0.001$), and the change was evident since day 2. Olanzapine but not asenapine significantly improved the MADRS score in comparison to placebo. This improvement was evident since day 7. Olanzapine but not asenapine improved mixed patients also. More patients under olanzapine and asenapine responded in comparison to placebo (50 % vs. 42.3 % vs. 25.2 %, $p<0.01$). The picture was similar concerning the remission rates. The dropout rate was similar in the three treatment arms (30.9 % vs. 37.1 % vs. 38.5 %); however, fewer patients dropped out because of lack of efficacy in the olanzapine group (5.8 % vs. 8.2 % vs. 16.3 %). Also the fewer patients under olanzapine dropped out because of adverse events in comparison to asenapine and similar to placebo (4.2 % vs. 10.3 % vs. 6.7 %). EPS were reported in numerically more olanzapine- and asenapine-treated patients in comparison to placebo (7.9 % vs. 7.2 % vs. 2.9 %). The most frequent adverse effects of olanzapine included sedation, dry mouth, dizziness, somnolence and weight gain (McIntyre et al. 2009a). The second one was again an international multicentre RCT of 3-week duration which included 488 acutely manic or mixed BD patients (rapid cycling excluded) and studied the efficacy and safety of olanzapine (5–20 mg/day; $N=205$) vs. asenapine (10–20 mg/day; $N=185$) vs. placebo ($N=98$). Olanzapine and asenapine were superior to placebo at day 21 (−14.6 vs. −11.5 vs. −7.8, $p<0.01$). For both medication arms the treatment effect was significant since day 2. Olanzapine but not asenapine significantly improved the MADRS score at endpoint. The response rate of olanzapine, but not of asenapine, was superior to that of placebo (54.7 % vs. 42.6 % vs. 34 %). This was true also for remission rates. The dropout rate was lower in the olanzapine arm (21.5 % vs. 33 % vs. 41.8 %). Fewer patients in the olanzapine arm discontinued because of lack of efficacy (6.3 % vs. 7.6 % vs. 14.3 %) or adverse events (3.4 % vs. 9.2 % vs. 4.1 %). Most frequent adverse events related with olanzapine treatment were somnolence, dizziness, sedation and EPS, while with asenapine they were somnolence dizziness, sedation and EPS. More EPS in comparison to placebo were registered in the olanzapine group but lower in comparison to asenapine (6.8 % vs. 10.3 % vs. 3.1 %). Weight gain was significantly more frequent in both treatment arms in comparison to placebo, but it was more pronounced in the olanzapine arm (19.0 % vs. 7.2 % vs. 1.2 %) (McIntyre et al. 2010b).

One 3-week US multicentre study in 329 manic or mixed hospitalized patients without psychotic features compared olanzapine (5–20 mg/day; $N=165$) vs. risperidone (1–6 mg/day; $N=164$). The authors reported only MMRM analysis (not

LOCF), and according to it, there was no difference between the two treatment arms in terms of YMRS, HAM-D and MADRS change. The response rate was also similar (62.1 % vs. 59.5 %), while there was a tendency more for olanzapine-treated patients to remit (38.5 % vs. 28.5 %; $p=0.07$). The effect on rapid cycling patients was similar to the rest of patients. Significantly less olanzapine-treated patients dropped out (21.3 % vs. 33 %; $p=0.019$), but the dropout rates because of adverse events and lack of efficacy were similar (5.4 % vs. 8.5 % and 4.2 % vs. 4.2 %, respectively). Olanzapine-treated patients experienced greater elevations in liver function enzymes, dry mouth and increase in weight, while risperidone-treated patients were more likely to experience prolactin elevation and sexual dysfunction (Perlis et al. 2006a).

Finally the NCT00329108 unpublished study of olanzapine (15–20 mg/day) vs. ziprasidone (120–160 mg/day) was stopped prematurely, after recruiting only 29 patients, and did not report any efficacy results (NCT00329108 study results 2009).

Olanzapine was found to have similar efficacy with risperidone in patients without psychotic features, in terms of YMRS, HAM-D and MADRS change. The two agents were also equal in the subgroup of rapid cycling patients. Fewer olanzapine-treated patients dropped out, but there was more weight gain in the olanzapine group (Perlis et al. 2006a). Finally the NCT00329108 unpublished study of olanzapine vs. ziprasidone was stopped prematurely (NCT00329108 study results 2009).

16.2.1.2.7 Quetiapine Versus Others

There are two studies comparing quetiapine with lithium (Bowden et al. 2005b; Li et al. 2008) and one with haloperidol (McIntyre et al. 2005) which were discussed above in the respected sections.

There is one study comparing quetiapine with paliperidone. That was an international multicentre 12-week (3 weeks with placebo) study which included 493 acutely manic or mixed patients and compared quetiapine IR (400–800 mg/day; $N=193$) vs. paliperidone ER (3–12 mg/day; $N=195$) vs. placebo ($N=105$). Both quetiapine IR and paliperidone ER significantly improved the YMRS at week 3 in comparison to placebo (−11.7 vs. −13.2 vs. −7.4; $p<0.001$). The treatment effect was evident as early as day 2 and lasted for the entire duration of the study, and it was similar for manic and mixed patients. Although a beneficial effect on total PANSS score was reported, no specific effects on the positive or negative subscales of the PANSS or on a depressive scale were included in the report. At week 3 more patients in the two treatment arms were responders in comparison to placebo (49 % vs. 55.8 % vs. 34.6 %). Similarly the remission rate was higher in both treatment arms in comparison to placebo at week 3 (47.4 % vs. 52.1 % vs. 28.8 %). This picture lasted for the entire duration of the study, and a similar picture was observed concerning the remission rates. The NNT for response or remission was 6–7 for quetiapine IR. At week 3 fewer patients under quetiapine IR or paliperidone ER dropped out in comparison to placebo (21.2 % vs. 20.5 % vs. 39 %). Fewer patients in the medication arms withdrew because of lack of efficacy in comparison to placebo, and these withdrawals were more in the quetiapine IR group in comparison to the paliperidone ER group (7.8 % vs. 3.1 % vs. 18.1 %). Dropout because of adverse

events was similar in the three arms. The most common treatment-emergent adverse events related to quetiapine were somnolence, sedation, dry mouth, headache and dizziness, and for paliperidone ER they were headache, somnolence and akathisia. At week 12 the body weight increase was more frequent in the quetiapine IR group (17 % vs. 8 %), but more patients under paliperidone ER switched to depression (13.9 % vs. 7.5 %) (Vieta et al. 2010b).

Conclusively, quetiapine is reported to be equal to lithium but with more dropouts and adverse events (Bowden et al. 2005b; Li et al. 2008). Also it is reported to be equal to haloperidol, with fewer dropouts and less frequent EPS, but less efficacious in psychotic patients. In contrast to haloperidol it had an effect on depressive symptoms (McIntyre et al. 2005). Quetiapine is reported to be equal to paliperidone, and both agents had a similar effect in manic and mixed patients. Body weight increase was more frequent in the quetiapine group, but more patients under paliperidone switched to depression (Vieta et al. 2010b).

16.2.1.2.8 Other Antipsychotics

There is also a one old 2-week study in 23 acutely manic inpatients (one admitted twice during two discrete episodes) that compared pimozide (6–32 mg/day; $N=12$) vs. chlorpromazine (200–1,600 mg/day; $N=12$). It reported that both agents led to clinical improvement, with a significant effect being noted within 24 h. Maybe chlorpromazine acted faster probably due to its greater sedative effect, but by 7 both drugs were equally effective. Sedation was the side effect most frequent with chlorpromazine, and EPS were more frequent with pimozide (Cookson et al. 1981).

All the studies concerning the rest of agents have been reported and discussed above; however, it is important to cite them again from a reverse angle. There are two studies which compared risperidone with haloperidol (Segal et al. 1998; Smulevich et al. 2005) and one vs. olanzapine (Perlis et al. 2006a). There is one study comparing aripiprazole with lithium (Keck et al. 2009) and two with haloperidol (Vieta et al. 2005a; Young et al. 2009), two studies comparing asenapine with olanzapine (McIntyre et al. 2009a, 2010b), one study comparing paliperidone with quetiapine (Vieta et al. 2010b), one unpublished study comparing ziprasidone with olanzapine (NCT00329108 study results 2009) and another one with haloperidol (Vieta et al. 2010c). Finally there are two studies comparing chlorpromazine with lithium (Platman 1970; Prien et al. 1972) and one with carbamazepine (Okuma et al. 1979).

16.2.1.2.9 Comparison of ECT Methods

In one 3-week study, 36 inpatients suffering from acute mania and referred for ECT were randomized to receive bifrontal (BFECT; $N=17$) or bitemporal (BTECT; $N=19$) ECT. None of the subjects were on mood stabilizers during the course of ECT. The YMRS scores showed faster decline in the BFECT than in the BTECT group. More patients in the BFECT group responded, and this happened significantly earlier than in the BTECT group. There were no significant differences between the groups in performance on cognitive function tests (Hiremani et al. 2008).

16.2.1.2.10 Conclusion of Comparison Studies

Overall, comparison studies suggest that the higher the efficacy, the more frequent the adverse events are. Although there are no sufficient data to support a big difference between agents, it seems that antipsychotics and lithium are more efficacious than valproate and carbamazepine unless you apply a loading strategy. Also it seems clear that antipsychotics act earlier in comparison to the other compounds. The effect on depressive symptoms is unclear, but it seems that haloperidol-treated patients might switch more often to depression. An effect of dosing on the abovementioned differences cannot be ruled out.

Earlier studies suggested that lithium could be specifically useful against the more 'classic' cases of euphoric mania, while antiepileptics might have a better efficacy in the rest of cases. This is not supported by more recent data (Fountoulakis et al. 2012d). A factor which could have affected the results is the well-known lithium discontinuation-related refractoriness (present probably in up to 15 % of patients) (Post et al. 1992). Because of this, patients enrolled in RCTs could constitute a sample more refractory to lithium treatment than expected. However even when samples enriched for lithium refractoriness were used, no inferiority of lithium to the other agent was documented (Bowden et al. 1994).

16.2.1.3 Combination and Add-On Treatment

A number of studies examine the efficacy and safety of agents given not as monotherapy but combined. This simultaneous administration of agents is given under a variety of conditions concerning the study sample, ranging from patients being refractory to a baseline treatment to absolutely usual patients. In the first instance, an agent is used as adjunct or add-on therapy on a pre-existing treatment to which the patient has shown unsatisfactory response. The definition of this unsatisfactory response varies widely, from explicitly recruiting some sort of refractory patients to simply demand pretreatment with the baseline therapy for at least 1–2 weeks, and still the patients fulfil the inclusion criteria. In the second instance, both the baseline agent and the second one which is compared with placebo are started simultaneously with the initiation of the trial. In this case the study tests a combination treatment against monotherapy. Although essentially both designs provide information on how to treat patients with unsatisfactory response to monotherapy, the conclusions and the generalizability differ, since studies on samples which include only refractory or partial responders (add-on studies) are more sensitive to the effect of the joint treatment in comparison to combination studies.

16.2.1.3.1 Combination Treatment

A summary of combination treatment data for the treatment of acute mania is shown in Table 16.3.

Carbamazepine Combinations

A 6-week international trial of olanzapine (10–30 mg/day; $N=58$) vs. placebo ($n=60$) on carbamazepine (400–1,200 mg/day) followed by open-label, 20-week olanzapine plus carbamazepine ($N=86$) reported no significant differences in

efficacy measures between treatment groups, but at 6 weeks triglyceride levels were significantly higher ($p=0.008$), and potentially clinically significant weight gain (≥7 %) occurred more frequently in the combined olanzapine and carbamazepine group (24.6 % vs. 3.4 %, $p=0.002$). Carbamazepine reduced olanzapine concentrations, but olanzapine had no effect on carbamazepine concentrations. Both agents were started simultaneously, and the results do not support the utility of such a treatment strategy (Tohen et al. 2008a). It should be noted that carbamazepine significantly reduces the serum concentration levels of many other agents.

A second 12-week double-blind, randomized, placebo-controlled study from China in 111 patients with acute mania randomized them to carbamazepine (300–800 mg/day; $N=43$) vs. carbamazepine plus the herbal Free and Easy Wanderer Plus (FEWP; 36 g/day; $N=46$) vs. placebo ($N=22$). At endpoint both carbamazepine arms produced significantly greater improvement on YMRS score, and the improvement was present already at week 4, but they did not differ from each other (−22.9 vs. −25.4 vs. −17). In terms of response rates, more patients in the carbamazepine arms were superior to placebo (87.8 % vs. 93 % vs. 57.1 %, $p=0.012$). Interestingly, although there was no difference between the two carbamazepine groups concerning the carbamazepine dosage, fewer patient under the combination dropped out (25.6 % vs. 13 % vs. 40.9 %), and this was also true concerning dropout because of lack of efficacy (7 % vs. 4.3 % vs. 27.3 %). Depressed and manic patients were pooled for the analysis of adverse events, and the adverse events occurring in over 5 % of the patients in any treatment group were dizziness, laboratory testing abnormality, skin rash, headache, fatigue, blurred vision, somnolence and nausea. Compared to carbamazepine monotherapy, patients in the combination therapy had a lesser incidence of dizziness (18.2 % vs. 7.9 %; $p=0.069$) and fatigue (9.1 % vs. 1.1 %; $p=0.038$). No difference in the incidence of other adverse events was found between the combination therapy and carbamazepine monotherapy. Although this study supports the efficacy of carbamazepine during the acute manic phase, the low carbamazepine dosage, in combination with the possible dramatic reduction of carbamazepine levels when co-administered with FEWP, plus the unusually high response rate even in the placebo group and the unusually low dropout rate, makes conclusions difficult. Technically it does not support the use of FEWP in acute mania, but a number of other interpretations also exist, for example, that adding FEWP compensates for the drop in carbamazepine levels (Zhang et al. 2007).

FGAs Combinations

One 3-week study in 136 hospitalized patients with acute mania utilized the adding of valproate (20 mg/kg; $N=69$) vs. placebo ($N=69$) on FGAs (preferably haloperidol and/or perazine). The valproate group had a higher response rate (70 % vs. 46 %; $p=0.005$). The mean neuroleptic dose declined continuously in the valproate group, whereas only slight variations were observed in the placebo group, and the difference was statistically significant ($p=0.0007$) for study weeks 2 and 3. Premature discontinuations occurred in only 13 % of the patients (Muller-Oerlinghausen et al. 2000).

Haloperidol Combinations

A 5-week study on 23 patients with carbamazepine ($N=23$) vs. placebo ($n=20$) on haloperidol suggested a superior performance in the combination group in terms of change in the Brief Psychiatric Rating Scale ratings (Klein et al. 1984). Another 3-week study in 21 severely ill manic inpatients investigated the comparative efficacy of lithium (up to 900 mg/day; $N=7$) vs. haloperidol (up to 30 mg/day; $N=7$) vs. a combination of haloperidol–lithium ($N=7$). All medications were initiated simultaneously. Subjects on haloperidol and the haloperidol–lithium combination were significantly improved after 7 days in comparison to the lithium-treated group. The haloperidol and the haloperidol–lithium combination groups did not differ from each other, either in degree of improvement or in side effects, and were superior to lithium monotherapy. Conclusively, that study suggested that combining haloperidol with lithium was not superior to haloperidol alone (Garfinkel et al. 1980). However, a more recent study reported that the combination of lithium with haloperidol at low dosage (5 mg/daily) but not the combination with haloperidol at high dosage (25 mg/daily) increased the efficacy against acute mania. In contrast, the combination of haloperidol with lorazepam had no added effect neither on the low nor on the high dosage (Chou et al. 1999).

Overall the data on combinations of agents with haloperidol vs. haloperidol monotherapy are equivocal, and the results might depend on the haloperidol dosage.

Lithium Combinations

As mentioned above, a 3-week study in 21 severely ill manic inpatients investigated the comparative efficacy of lithium (up to 900 mg/day; $N=7$) vs. haloperidol (up to 30 mg/day; $N=7$) vs. a combination of haloperidol–lithium ($N=7$). Subjects on haloperidol and the haloperidol–lithium combination were significantly improved after 7 days in comparison to the lithium-treated group. Conclusively, that study suggested that the combination of haloperidol plus lithium is superior to lithium alone (Garfinkel et al. 1980). The lithium plus haloperidol combination was tested vs. lithium plus lorazepam in 20 hospitalized patients. There was no evidence for a significant difference between the two treatment groups in the magnitude of or time to response (5.0 ± 0.82 days for haloperidol; 6.5 ± 0.93 days for lorazepam). Of the patients who were terminated from the protocol early, nonresponse was the primary reason in the lorazepam group, while side effects were the reason in the haloperidol group (Lenox et al. 1992). It was also tested vs. carbamazepine plus lithium in 33 hospitalized manic patients which were withdrawn from psychoactive medications for 2 weeks after which they were randomized to double-blind treatment. Again the two groups were similar. However the haloperidol group had more EPS that were major reasons for dropout, whereas carbamazepine group patients were more often noncompliant and initially required more rescue medications (Small et al. 1995). Overall the haloperidol plus lithium combination seems to be somewhat more effective than lithium monotherapy and other combinations with lithium but with more adverse effects.

A 3-week trial on with a manic or mixed episode was randomized to receive ziprasidone (80–160 mg/day; $N=101$) vs. placebo ($N=103$) on top of lithium

(serum levels 0.8–1.2 mEq/l). All medications were initiated since the beginning of the study. There was no superiority of the ziprasidone group over placebo at endpoint concerning the MRS (Weisler et al. 2003; Bowden 2005).

A 4-week study from Brazil in 180 inpatients in a manic episode with or without psychotic features (mixed and rapid cycling excluded) compared fixed oral doses of allopurinol (600 mg/day; $N=60$) vs. dipyridamole (200 mg/day; $N=60$) vs. placebo ($N=60$) as adjunct treatment on lithium. All medications started together in all the study arms. Allopurinol resulted in greater mean reductions in YMRS scores from baseline to day 21 ($p<0.001$) and day 28 ($p=0.003$) compared with placebo. Remission rates were significantly higher for allopurinol compared with dipyridamole and placebo ($p=0.008$). The dipyridamole group did not differ from placebo. The presence of psychotic symptoms did not influence the results. The dropout rate was similar in the three groups. Decrease in plasma uric acid levels showed a significant positive association with antimanic effects in the allopurinol group ($p<0.001$) (Machado-Vieira et al. 2008).

Finally, a 6-week study on 40 manic inpatients allocated to tamoxifen (80 mg/day; $N=$) vs. placebo on top of lithium (1–1.2 mEq/l) B) reported significant difference in favour of the tamoxifen group ($p=0.02$) concerning the YMRS and the total PANSS without any difference on adverse events except for fatigue that occurred more often in the tamoxifen group simultaneously (Amrollahi et al. 2010).

Overall the combination data support the conclusion that all the combinations which included lithium (haloperidol, lorazepam, carbamazepine, ziprasidone, tamoxifen, allopurinol) were proven superior to lithium alone, with the exception of the dipyridamole plus lithium. Most of these combinations had more adverse events in comparison to monotherapy, and there was a trend that the more effective the combination, the more adverse events it showed.

Lithium or Valproate Combinations

A number of trials investigate the addition of an agent on top of lithium or valproate, since these two constituted the backbone of the treatment of bipolar disorder for decades.

A multicentre trial from the USA on 117 patients on mania, hypomania or mixed episodes of gabapentin (900–3,600 mg/day; $N=58$) vs. placebo ($N=59$) on lithium or valproate or both (it included a 2 weeks placebo lead-in) was negative (Pande et al. 2000). Similarly negative was a 3-week multicentre trial on 156 patients with manic or mixed episode which tested the administration of risperidone (1–6 mg/day; $N=52$) vs. haloperidol (2–12 mg/day; $N=53$) vs. placebo ($N=51$) as combination therapy with lithium (29 %) or divalproex (71 %). For the whole sample a significantly greater reduction in the YMRS score was observed in both combination medication groups in comparison to placebo (−14.3 vs. −13.4 vs. 8.2); however, the small subsample of patients which did not receive mood stabilizers until the start of the trial precluded any conclusion for this specific subgroup ($N=17$, −11.3 vs. $N=17$, −10.1 vs. $N=19$, −9.4). The trial was discontinued by 49 % of the placebo group patients, 35 % of the risperidone group patients and 53 % of the haloperidol group patients (Sachs et al. 2002).

A small 4-week study on 13 women with acute mania/hypomania which were given tamoxifen (40 mg/day; $N=5$) or medroxyprogesterone acetate (MPA; 20 mg/

day; $N=4$) or placebo ($N=4$) as add-on to lithium and/or valproate reported that at endpoint only the tamoxifen group manifested a significant change from baseline in the CARS-M score (−22.2 vs. −13 vs. −8.5). No effect on the PANSS positive subscale was evident in any group. Although it is not reported specifically, the study sample was not constituted of refractory patients, and all medications were started simultaneously. The small study sample precludes any strong conclusions (Kulkarni et al. 2006).

Finally, a 12-week study in 324 manic or mixed episodes with asenapine (5–10 mg; $N=158$) vs. placebo (N = 166) on lithium or valproate reported that adjunctive asenapine significantly improved the YMRS score at week 3 and the response and remission rates at week 12 (Szegedi et al. 2012).

Conclusively, the data are in support of combining lithium or valproate with asenapine or tamoxifen.

Valproate Combinations

One 3-week study on 88 manic patients evaluated folic acid (3 mg/day; $N=44$) vs. placebo ($N=44$) on top of valproate. There was a statistically significant difference in the YMRS results between the case and control groups after 3 weeks of treatment ($p=0.005$), although the analysis of the results was not the standard. Only four patients dropped out (Behzadi et al. 2009). Also, one small study on 15 manic patients which investigated the use of omega-3 fatty acids as combination therapy with valproate was negative (Chiu et al. 2005).

Risperidone Combinations

A 3-week study on 81 partially responding acutely manic patients which were receiving a mood stabilizer for at least 2 weeks prior to study entry allocated them to risperidone ($n=42$) vs. placebo ($n=39$) on top of lithium, valproate or carbamazepine. The results suggested that there was no difference between arms in terms of change in the YMRS score (−14.9 vs. 13.2). It should be noted that in carbamazepine-treated patients the risperidone plasma levels were 40 % lower. The incidence of adverse events was similar in both groups (Yatham et al. 2003).

Conclusively, there are few but still important data suggesting that specific combinations are superior to monotherapy in non-refractory or otherwise selected samples, although it is difficult to assess the quality of many study samples. In spite of the very small number of trials and the problems with the data quality, one could generalize that the combination of an antipsychotic plus lithium or valproate is superior to lithium or valproate alone. Tamoxifen and probably allopurinol are also valuable agents to use in combination with other treatment modalities.

16.2.1.3.2 Add-On Treatment

Add-On to Haloperidol

A small 5-week study on 12 refractory patients with acute mania of phenytoin ($N=6$) vs. placebo ($N=6$) on haloperidol reported that there was more improvement in the patients receiving phenytoin (Mishory et al. 2000).

Add-On to Lithium

An 8-week trial on 52 incomplete responders to lithium utilized the addition of 600–1,200 mg/day carbamazepine ($N=26$) or oxcarbazepine ($N=26$) during maintenance treatment. All patients completed the study. Although this trial was on patients in the 'maintenance' phase the design and the results are more relevant to the acute manic phase. The study sample constituted of manic, mixed and depressed patients. Both groups improved with the addition of either drug, but those receiving oxcarbazepine improved significantly more on the YMRS score at endpoint. Oxcarbazepine improved also the HAM-D and the MADRS score and exhibited better tolerability in comparison to carbamazepine (Juruena et al. 2009).

Add-On to Lithium or Valproate

A 3-week multicentre trial on 156 patients with manic or mixed episode tested the administration of risperidone (1–6 mg/day; $N=52$) vs. haloperidol (2–12 mg/day; $N=53$) vs. placebo (N=51) as add-on therapy on lithium (29 %) or divalproex (71 %). The results suggested a significantly greater reduction in the YMRS score in both add-on medication groups in comparison to placebo (−14.3 vs. −13.4 vs. 8.2). Especially among patients who were receiving mood stabilizers at the start of the trial ('breakthrough' patients), the mean total score on the YMRS decreased more in the medication add-on groups in comparison to placebo ($N=34$, −15.7 vs. $N=33$, −14.9; $N=28$, −7.4). The trial was discontinued by 49 % of the placebo group patients, 35 % of the risperidone group patients and 53 % of the haloperidol group patients (Sachs et al. 2002).

In another 6-week trial on 344 partially responsive manic or mixed patients, olanzapine (5–20 mg/day) vs. placebo as add-on treatment on valproate or lithium was tested, and the results suggested that that olanzapine co-therapy improved the patients' YMRS total scores significantly more than monotherapy (−13.11 vs. −9.10; $p=0.003$). A similar picture was there concerning the response rate (67.7 % vs. 44.7 %; $p<0.001$). Olanzapine co-therapy improved also the HAM-D. Treatment-emergent symptoms that were significantly higher for the olanzapine co-therapy group included somnolence, dry mouth, weight gain, increased appetite, tremor and slurred speech (Tohen et al. 2002b).

In a 3-week combination treatment study, patients under lithium (0.7–1.0 mEq/l) or valproate (50–100 μg/ml) were randomized to receive quetiapine IR (up to 800 mg/day; $N=91$) or placebo ($N=100$). Patients should have been treated with li/val at 7 days prior to randomization. More patients in the quetiapine group completed the study (61.5 % vs. 49 %). A significantly greater mean reduction in the YMRS score was observed at endpoint in the quetiapine group (−13.76 vs. −9.93; $p=0.021$). Also the response rate was significantly higher in the quetiapine group (54.3 % vs. 32.6 %; $p=0.005$), as was the remission rate (45.7 % vs. 25.8 %; $p=0.007$). Common adverse events in the quetiapine group included somnolence, dry mouth, asthenia and postural hypotension (Sachs et al. 2004). Another 3-week study on 402 partial responders with acute mania tested the adding of quetiapine IR up to 800 mg/day ($N=197$) vs. placebo ($N=205$) on lithium (serum concentration 0.7–1.0 mEq/l) or valproate (serum concentration 50–100 μg/ml). The improvement

in the YMRS in the quetiapine group was significant at day 21 (−15.29 vs. −2.19; $p<0.05$). Similarly, the quetiapine group was superior concerning the response rate (55.7 % vs. 41.6 %; $p<0.01$). More patients in the quetiapine group completed the trial, and there was no difference in discontinuation rates due to adverse events between the two groups. Common adverse events in the quetiapine group were somnolence, dry mouth and asthenia (Yatham et al. 2004). A third study utilizing quetiapine was a 6-week study on 200 partial responders with acute mania which tested the adding of quetiapine IR up to 800 mg/day ($N=104$) vs. placebo ($n=96$) on lithium (serum concentration 0.7–1.0 mEq/l) or valproate (serum concentration 50–100 µg/ml). There was no difference in the YMRS change between groups (Yatham et al. 2007).

A 6-week multicentre study included 384 partial responders experiencing a manic or mixed episode (with or without psychotic features) and utilized the addition of aripiprazole (15–30 mg/day; $N=253$) vs. placebo ($N=131$) on lithium (0.6–1.0 mmol/l) or valproate (50–125 µg/ml). The mean improvement from baseline in YMRS total score at week 6 was significantly greater with aripiprazole (−13.3 vs. −10.7), and the difference was present already since week 1. There was also a superiority concerning the response rate at week 6 (62.8 % vs. 48.5 % for both the lithium and valproate groups). Discontinuation rates due to adverse events were higher with aripiprazole than with placebo (9 % vs. 5 %). Akathisia was the most frequently reported extrapyramidal symptom-related adverse event and occurred significantly more frequently among those receiving aripiprazole (18.6 % vs. 5.4 %). There were no significant differences between treatments in weight change from baseline to week 6 (+0.55 kg vs. +0.23 kg) (Vieta et al. 2008c).

A 3-week multicentre US study on 448 patients with acute manic or mixed episode utilized ziprasidone (40–80 mg/day; $N=226$ or 80–160 mg/day; $N=232$) vs. placebo ($N=222$) on top of lithium or divalproex. There was no difference at endpoint in the change in the YMRS scores from baseline (–11.0 vs. −10.2 vs, −9.5), and similarly there was no difference in any of the outcomes (Sachs et al. 2012a, b).

A 12-week study in 287 patients in a manic or mixed episode to investigate the efficacy and safety of topiramate (50–400 mg/day; $N=143$) vs. placebo ($N=144$) as adjunctive therapy on valproate (serum levels 45–100 mg/l) or lithium (serum levels 0.5–1.2 mEq/l) reported that at endpoint there was no difference in the YMRS score change in the two groups (−10.1 vs. −9.6). Similarly there was no difference concerning the response rates (39 % vs. 38 %) and the secondary outcomes. Topiramate did not worsen mania or induce depression. Paraesthesia, diarrhoea and anorexia were more common in the topiramate group. However the topiramate group achieved greater reductions than the placebo group in body weight (−2.5 vs. 0.2 kg, $p<0.001$) and body mass index (−0.84 vs. 0.07 kg/m(2), $p<0.001$) (Roy Chengappa et al. 2006).

A 6-week study on 300 patients with acute mania or mixed episode (33 % mixed; with or without psychotic features) which were allocated to paliperidone ER (3–12 mg/day; $N=150$) vs. placebo ($N=150$) in addition to lithium (38 %) or valproate (62 %) reported that there was no significant difference between groups in terms of YMRS change (−14.3 vs. −13.2; $p=0.16$) or in any of the secondary

outcomes. More patients under the combination treatment manifested an adverse event (70 % vs. 54 %) (Berwaerts et al. 2011).

Finally, a 12-week international multicentre study in 324 patients experiencing manic (60 %) or mixed (40 %) episodes evaluated the efficacy and safety of asenapine (10–20 mg/day; $N=158$) vs. placebo ($N=166$) as adjunctive treatment on lithium or valproate. Adjunctive asenapine significantly improved the YMRS score at week 3 (−10.3 vs. −7.9; $p=0.026$). The response rates were similar at week 3 (32 % vs. 27 %) but significantly better with asenapine at week 12 (47.7 % vs. 34.4 %; $p=0.0152$). The remission rates were significantly greater with asenapine at weeks 3 (33.5 % vs. 21.5 %; $p=0.0158$) and 12 (43.2 % vs. 30.1 %; $p=0.0148$). Some but not all of the secondary outcomes were significantly better with asenapine at weeks 3 and 12. Overall discontinuation rates were higher with adjunctive placebo than with adjunctive asenapine. Treatment-emergent adverse events related with asenapine treatment were sedation, somnolence, depressive symptoms, oral hypoesthesia and increased weight (Szegedi et al. 2012).

Overall, the data suggest that in patients who are refractory or partial responders to lithium or valproate, it is beneficial to add risperidone, haloperidol, olanzapine, quetiapine, aripiprazole and asenapine but not ziprasidone, topiramate or paliperidone.

Add-On to Lithium, Valproate or Carbamazepine

A 3-week study on 60 partially responding acutely manic patients which were receiving a mood stabilizer for at least 2 weeks prior to study entry allocated them to risperidone ($n=26$) vs. placebo ($n=34$) on top of lithium, valproate or carbamazepine. The results suggested that there was no difference between arms in terms of change in the YMRS score (−13.8 vs. 7.1); however, there was a numerical difference, and the small study subsample precluded significance. Again it should be noted that in carbamazepine-treated patients the risperidone plasma levels were 40 % lower. The incidence of adverse events was similar in both groups (Yatham et al. 2003).

Add-On to Lithium, Valproate or Carbamazepine or Atypical Antipsychotics

A 6-week study randomized 27 manic or mixed subjects to allopurinol (600 mg/day; $N=15$) vs. placebo ($N=12$) on top of lithium, valproic acid, carbamazepine or atypical antipsychotic medications. Allopurinol augmentation did not show a statistically significant improvement over placebo. Subjects with restricted caffeine use showed a greater effect size compared to caffeine users (Fan et al. 2012).

Add-On ECT

There is only one sham-controlled trial of ECT as adjunctive treatment on chlorpromazine (600 mg/day) in 30 acutely manic patients. That study supported the efficacy of ECT with a faster rate of improvement (Sikdar et al. 1994).

Add-On to Treatment as Usual

One small 8-week study in 21 ambulatory mild-to-moderate manic patients with insomnia evaluated the efficacy and tolerability of ramelteon (fixed-dose 8 mg/day;

$N = 10$) vs. placebo ($N = 11$). There was no difference between groups in terms of outcome concerning the manic symptoms. However, ramelteon was associated with improvement in a global rating of depressive symptoms and was also well tolerated and associated with no serious adverse events (McElroy et al. 2010d).

Overall, the data on partial responders or refractory patients support the addition of specific antipsychotics on top of lithium or valproate and also the use of allopurinol and the combination of lithium with carbamazepine or oxcarbazepine.

Other Add-On Options

A recent placebo-controlled 4-week RCT in 180 acutely manic patients supported the efficacy and safety of the purinergic agents allopurinol (600 mg/day) and dipyridamole (200 mg/day) as adjunctive to lithium in acute bipolar mania (Machado-Vieira et al. 2008). Folic acid was also found to be useful as an adjunct to valproate against acute mania (Behzadi et al. 2009). There is one 5-week trial from Israel on 32 recently admitted manic inpatients which compared valnoctamide (600–1,200 mg/day; $N = 15$) vs. placebo ($N = 17$) on top of risperidone (1–6 mg/day). All medications were started at day 1. In all efficacy measures the valnoctamide plus risperidone combination was more effective than risperidone plus placebo from week 3 to week 5. Valnoctamide is an anticonvulsant analogue of valproate that does not undergo biotransformation to the corresponding free acid and in mice has been shown to be distinctly less teratogenic than valproate (Bersudsky et al. 2010). A pilot 8-week study in 21 acutely manic outpatients on the usefulness of adjunctive ramelteon against acute mania/mixed failed to produce a positive result for the agent (McElroy et al. 2010d).

16.2.1.4 Post Hoc Analyses and Meta-analytic Studies

16.2.1.4.1 Post Hoc Analyses

Olanzapine

A secondary analysis of a trial on olanzapine (Tohen et al. 2000) reported that olanzapine is effective in acutely manic or mixed patients irrespective of whether or not they have failed to respond to another treatment in the past (Baker et al. 2002). The data of two trials of olanzapine in acute mania (Tohen et al. 1999, 2000) were pooled and analysed in combination. The sample was stratified in terms of gender, age, episode type, psychotic features, substance abuse and specific clinical features. The results showed significant antimanic efficacy in all subgroups. There was somewhat superior efficacy of olanzapine in patients who were younger at illness onset, without prior substance abuse and had not previously received antipsychotic treatment (Baldessarini et al. 2003). Another reanalysis of the pooled data of these two specific trials (Tohen et al. 1999, 2000) reported that olanzapine monotherapy resulted in significant clinical improvement in over half of the patients, and just under 20 % of them achieved a near complete remission of both manic and accompanying depressive symptoms (Chengappa et al. 2003). A post hoc analysis of a study which compared olanzapine (5–20 mg/day) to divalproex sodium (500–2,500 mg/day) for

bipolar manic or mixed episodes ($N=251$) (Tohen et al. 2003c) classified patients at study entry as 'rapid cyclers' if they experienced at least four episodes within the last year. Olanzapine was proven superior in non-rapid cyclers, while both agents were equal in rapid cycling patients. Under olanzapine, non-rapid cycling patients improved more than rapid cycling, while under divalproex both groups improved to a similar extent. Overall rapid cycling patients did less well over long-term treatment than non-rapid cycling patients. Conclusively this post hoc analysis suggests that olanzapine has a broader efficacy in the treatment of acutely manic or mixed patients, while divalproex matches the efficacy of olanzapine only in rapid cycling patients (Suppes et al. 2005).

Quetiapine

An a priori-defined combined analysis of data from two placebo-controlled studies (McIntyre et al. 2005; Bowden et al. 2005b) reported that a significant improvement in the quetiapine group (both psychotic and nonpsychotic patients) vs. placebo concerning the change in YMRS score was observed already since day 4 ($p=0.021$), and the improvement continued until the end of the trials and concerned all YMRS individual items. The response and remission rates were also higher for the quetiapine group. Quetiapine significantly improved the PANSS total and the positive subscale as well as the MADRS score ($p<0.001$). Treatment with quetiapine was related with the emergence of somnolence, dry mouth, weight gain and dizziness (Vieta et al. 2005b).

Risperidone

A post hoc analysis of one multicentre risperidone study from India (Khanna et al. 2005) of 3-week duration which included 291 acutely manic or mixed BD patients (rapid cycling excluded) and assessed the efficacy and safety of risperidone (1–6 mg/day, $N=146$) vs. placebo ($N=145$) reported that more patients under risperidone achieved remission (42 % vs. 13 %), and fewer dropped out (11 % vs. 29 %) especially because of lack of efficacy (5 % vs. 15 %). The dropout because of adverse events was similar in the two patient groups. This analysis did not report adverse events or the effect of the intervention in any other scale except YRMS in terms of remission alone (Gopal et al. 2005).

Asenapine

Exploratory pooled post hoc analyses from two trials of asenapine in acute mania (McIntyre et al. 2009a, 2010b) evaluated the efficacy of asenapine and olanzapine on depressive symptoms, in those patients with significant baseline depressive symptoms. In the original trials, 977 patients were randomized to flexible-dose sublingual asenapine (10–20 mg/day), oral olanzapine (5–20 mg/day) or placebo. The pooled analysis identified three populations by using baseline depressive symptoms: a. MADRS score ≥ 20 ($N=132$), b. CGI for Bipolar Disorder-Depression (CGI-BP-D) scale severity score ≥ 4 ($N=170$) and c. diagnosis of mixed episodes ($N=302$). The results suggested that the decreases in MADRS total score were statistically greater with asenapine vs. placebo at days 7 and 21 in all populations,

while the differences between olanzapine and placebo were not significant. Olanzapine manifested some efficacy on the basis of the decreases in CGI-BP-D scores, but its results appeared to be less consistent (Szegedi et al. 2011). A second analysis confirmed its efficacy in mixed episodes (Azorin et al. 2013). Another meta-analyses suggested that asenapine had an effect on every individual YMRS item, and thus it has an effect on the core of mania (Cazorla et al. 2013).

Aripiprazole

Another analysis was designed to assess the efficacy and safety of aripiprazole in subpopulations of patients with acute manic or mixed episodes. The 516 patients from two trials (Sachs et al. 2006; Keck et al. 2003a) were stratified by severity, episode type, presence or absence of psychotic features, episode frequency, age, gender, and baseline severity of depressive symptoms. Analyses concerning safety and adverse event analyses were also performed. The results suggested that aripiprazole significantly improved the YMRS total scores in comparison to placebo in all subpopulations except the >55 years age group. The treatment-emergent adverse events profile differed between genders and age groups (Suppes et al. 2008a).

Ziprasidone

A pooled data analysis from two similarly designed trials on ziprasidone in acute bipolar mania (Keck et al. 2003b; Potkin et al. 2005) selected all patients with scoring ≥2 on at least two items of the extracted HAM-D. These 179 patients (ziprasidone, $N=124$; placebo, $N=55$) were considered to meet criteria for dysphoric mania and were included in the post hoc analysis. Patients treated with ziprasidone manifested a significant reduction in their HAM-D scores beginning at day 4 in comparison to placebo ($p<0.05$). They had also significant improvements on the MRS score and all secondary efficacy measures, and had significantly higher response and remission rates compared with placebo (Stahl et al. 2010). Another pooled analysis of the same two trials of ziprasidone (Keck et al. 2003b; Potkin et al. 2005) reported that significantly greater antipsychotic effects were observed with ziprasidone already by day 4, and the magnitude of improvement increased significantly with time, and it concerned all patients and predicted subsequent acute manic episode remission (Ketter et al. 2010).

Lithium

A post hoc analysis of a lithium trial (Bowden et al. 1994) confirmed the efficacy of lithium in classic manic but not mixed patients. All other effects were negative (Swann et al. 1997).

16.2.1.4.2 Meta-analyses

The first meta-analysis included only randomized controlled clinical trials with a double-blind assessment of outcomes, and lithium levels were required to be within the therapeutic range of 0.4–1.5 mmol/l. It compared lithium vs. valproate and carbamazepine and reported that there is no significant difference between them; however, there was a general tendency in favour of the antiepileptics with regard to

adverse events and treatment tolerance. These results questioned the widely accepted opinion that lithium is the first choice and antiepileptics follow (Emilien et al. 1996).

More recent meta-analytic studies suggest that the efficacy of second-generation antipsychotics is established both as monotherapy and as add-on therapy to mood stabilizers. An early comparison of second-generation antipsychotics found aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone superior to placebo as monotherapy but failed to detect any differences between them (Perlis et al. 2006b). Another study compared second-generation antipsychotics with placebo, first-generation antipsychotics or mood stabilizers in the treatment of acute mania and reported that the second-generation antipsychotics were significantly more efficacious than placebo both as monotherapy and also as adjunct treatment on mood-stabilizing agents. They were associated with EPS and somnolence (Scherk et al. 2007). Another one tested whether combination treatment is superior to monotherapy and reported that significant reductions in YMRS scores were shown with haloperidol, olanzapine, risperidone and quetiapine as adjunctive treatment on a mood stabilizer vs. a mood stabilizer alone. Also significantly more patients under cotherapy responded. However, the combination treatment manifested more adverse events (especially weight gain) and lower tolerability (Smith et al. 2007). One meta-analysis suggested that that antimanic agents are roughly equal in efficacy against acute mania (Tamayo et al. 2010); however, two others reported that second-generation antipsychotics are superior to antiepileptics, but this should be balanced against increased adverse events (EPS, somnolence and weight gain) especially in youth (Correll et al. 2010; Tarr et al. 2010), while a more recent one reported that haloperidol shows a faster onset of antimanic action in comparison to second-generation antipsychotics (Goikolea et al. 2013a) but also the most likely to switch patients to depression (Goikolea et al. 2013b). Olanzapine and aripiprazole are confirmed to be efficacious against psychotic features (Baldessarini et al. 2003; Fountoulakis et al. 2009; Suppes et al. 2008a). One meta-analysis reported that combination treatment was more effective than monotherapy, studies outside the USA had higher effect size and the baseline YMRS predicted the outcome (Tarr et al. 2011) probably because of a structural coupling effect (Fountoulakis and Kontis 2012). Year of study publication was not associated with YMRS score change. Also the study size, number of study sites, YMRS score required for study entry, inclusion of patients with mixed mania or treatment resistance and inclusion of inpatients vs. outpatients had no significant influence on the outcome.

The review and meta-analysis of data available for oxcarbazepine suggests that although there are some positive data (Hirschfeld and Kasper 2004) the level of evidence is insufficient (Vasudev et al. 2011).

Two recent meta-analyses attempted to rank antimanic agents according to efficacy. The first one utilized the method of multiple treatments meta-analysis and reported that the ranking in terms of efficacy was haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate and ziprasidone. According to that meta-analysis, overall, antipsychotics were significantly more effective than mood stabilizers (Cipriani et al. 2011). However this meta-analysis has been criticized both concerning the overall methodology but also

concerning the incomplete list of RCTs which was utilized (Fountoulakis and Siamouli 2012). A more balanced meta-analysis confirmed that the response to antipsychotics was greater and more rapid in comparison to lithium, valproate or carbamazepine, but it did not confirm any difference between haloperidol and second-generation antipsychotics (Yildiz et al. 2010).

A meta-analysis which pooled data from nine randomized, double-blind, placebo-controlled, acute studies of ziprasidone reported that the discontinuation rate due to adverse events or 7 % or greater weight gain between ziprasidone and placebo was not significant in all psychiatric conditions. In acute mania the risk for akathisia with ziprasidone had a NNTH = 12, the risk for overall EPS had a NNTH = 12 and the reported somnolence had NNTH = 7 (Gao et al. 2013).

The number needed to treat to harm (NNTH) of ziprasidone relative to placebo was estimated when an RD was statistically significant. Results: The RD in discontinuation due to adverse events or 7 % or greater weight gain between ziprasidone and placebo was not significant in all three psychiatric conditions. The risk for akathisia with ziprasidone was significantly higher in BPD with an RD of 2.3 % (NNTH = 44) and in BPM with an RD of 8.4 % (NNTH = 12). Risk for overall EPS with ziprasidone was significantly higher in BPM with an RD of 8.7 % (NNTH = 12) and schizophrenia with an RD of 3.3 % (NNTH = 30). Risk of reported somnolence with ziprasidone was also significantly higher in BPD with an RD of 11.8 % (NNTH = 8), BPM with an RD of 14.3 % (NNTH = 7) and schizophrenia with an RD of 7 % (NNTH = 14). Dose-dependent increase in the risk for reported somnolence with ziprasidone was observed in BPD and schizophrenia. Conclusions: Ziprasidone was associated with significant differential adverse effects relative to placebo in BPM, BPD and schizophrenia with no significant difference in weight gain in all three groups. Self-reported somnolence was increased across the three conditions. Subjects with BPM were more vulnerable to EPS than those with BPD or schizophrenia.

Finally, a recent network meta-analysis reported that there is no superiority of any antimanic agent vs. another except for risperidone vs. aripiprazole and valproate. Aripiprazole, olanzapine, quetiapine, risperidone and valproate had less all-cause discontinuation rates than placebo. Sensitivity analysis by drug class indicated similar efficacy profiles for haloperidol, second-generation antipsychotics and mood stabilizers (Yildiz et al. 2014).

Overall, post hoc and meta-analytic studies confirm the superiority of antipsychotics vs. lithium, valproate and carbamazepine both in terms of faster onset of action but also in terms of the overall outcome in the treatment of acute mania. However they also confirmed that this higher efficacy comes with the cost of more frequent adverse events, mainly EPS, weight gain and somnolence. Olanzapine was proven efficacious against mixed episodes, depressive symptoms and psychotic features as well as in rapid cycling patients. Quetiapine was proven efficacious for all YMRS individual items, depressive symptoms and also against psychotic features. Asenapine was confirmed to be efficacious against depressive symptoms. Aripiprazole was found to have no effect in patients aged >55 years but is effective against psychotic symptoms. Ziprasidone was reported to be effective against

dysphoric mania. Meta-analytic studies also suggest that combination treatment is superior to monotherapy; however, they did not distinguish between add-on and combination studies and populations. The data of oxcarbazepine were found to be insufficient.

16.2.2 Acute Bipolar Depression

Bipolar depression is not well studied, in spite of the fact that it is the facet of BD responsible for most of the burden of the disease. Until not many years ago, it was mostly considered to be similar in clinical and neurobiological terms with 'endogenous' or 'melancholic' unipolar depression and was treated accordingly. The only reservation was that antidepressants might switch to the manic pole. Therefore, only a limited number of RCTs exist, and the common practice among clinicians is to carry the clinical data and wisdom from the treatment of unipolar to bipolar depression. However the data clearly suggest such an approach to be wrong.

The agents are listed below in a 'historical' sequence with lithium and anticonvulsants first, then antidepressants and finally with antipsychotics on the basis of the year of the first study they were investigated.

16.2.2.1 Monotherapy

A summary of monotherapy data for the treatment of acute bipolar depression is shown in Table 16.4.

16.2.2.1.1 Lithium

In spite of the widely spread belief that lithium is an effective treatment option against bipolar depression, there are no data in support of it. The earlier studies provided some positive data but are difficult to interpret (Mendels 1976; Stokes et al. 1971; Goodwin et al. 1969b, 1972; Greenspan et al. 1970; Noyes and Dempsey 1974; Noyes et al. 1974; Baron et al. 1975; Donnelly et al. 1978; Srisurapanont et al. 1995). There is only one rigorously conducted 8-week RCT (EMBOLDEN I) in 802 bipolar depressed patients (499 BD-I, 303 BD-II) which investigated the efficacy and tolerability of lithium (600–1,800 mg/day; $N=136$) vs. quetiapine (300 mg/day; $N=265$ or 600 mg/day; $N=268$) vs. placebo ($N=133$). The change in the mean MADRS total score at endpoint was not significant for lithium ($p=0.123$), while it was significant concerning both quetiapine groups ($p<0.001$) vs. placebo (−13.6 vs. −15.4 vs. −16.1 vs. −11.8). Quetiapine improved most of the MADRS individual items suggesting an effect on the core depressive symptoms, while lithium improved only 'inner tension' and 'reduced sleep'. A similar picture emerged with the HAM-D and the Hamilton Anxiety Scale. At endpoint, the response rate was not significant for lithium ($p=0.279$), but it was significant for the two quetiapine groups ($p<0.001$) in comparison to placebo (62.5 % vs. 68.6 % vs. 69.6 % vs. 55.8 %) and so were the remission rates (62.5 % vs. 69.8 % vs. 70.3 % vs. 55.0 %). The overall dropout rate was lower in the lithium group (14.4 % vs. 24.5 % vs. 23.5 % vs. 27.8 %), and this was in part due to a lower dropout rate in the lithium

group because of adverse events (5.1 % vs. 9.8 % vs. 13.1 % vs. 8.3 %). Concerning the dropout rate due to lack of efficacy, the lithium group had a rate similar to placebo, while the 600 mg quetiapine group had the lowest rate (4.2 % vs. 4.2 % vs. 0.7 % vs. 5.3 %). The most common adverse event with lithium treatment was nausea with lithium. A problem is that in this particular study the mean lithium serum levels were 0.61 mEq/l, with 34.9 % of patients having levels below 0.6 mEq/l, which are lower than the generally recommended. However a further post hoc analysis which included only patients with lithium levels >0.8 mEq/l ($N=34$) reported again no significant difference between lithium and placebo, and the numerical difference (−2.5 point of the MADRS scale) was similar to that of the whole lithium group vs. placebo (−1.8). The difference was not significant in patients who completed the study either. Quetiapine was significantly effective in BD-I but not in BD-II patients. It is unclear whether quetiapine or lithium are effective in rapid cycling patients although there is some signal for lithium (Young et al. 2010). It seems that in spite of these negative findings, it is reasonable to keep lithium in mind as a therapeutic option, and the authors believe the data are inconclusive.

16.2.2.1.2 Valproate

The efficacy and safety of divalproex was tested in an 8-week clinical trial in 25 outpatients with BD-I depression. These patients were randomized to receive either divalproex (rapidly titrated up to 2,500 mg/day, as tolerated, to a target serum level of 50–100 mg/dl; $N=13$) or placebo ($N=12$). Although the sample size was small and the analysis was not the standard, the results suggested that divalproex-treated patients had significant improvement in their depression as this was reflected in the change in HAM-D scores from baseline (−11.5 vs. −6.5; $p=0.002$) and anxiety ratings in comparison to placebo. More patients under divalproex remitted (46 % vs. 25 %). Apart from the small study sample, another limitation of this study was that most patients were male (Davis et al. 2005). Another 6-week small study on 18 acute non-refractory bipolar depressed patients investigated divalproex ER (target dose level 70–90 ng/dl; $N=9$) vs. placebo ($N=9$). The results suggested that the divalproex ER treatment group showed significantly greater reduction in the MADRS scores compared to placebo (−13.6 vs. −1.4; $p=0.003$), and the analysis of individual MADRS items supported an effect of divalproex ER on the core symptoms of depression (Ghaemi et al. 2007).

An exploratory evaluation of the efficacy and safety of divalproex ER with a 6-week trial on 54 mood stabilizer-naïve patients with BD-I ($N=20$) or BD-II ($N=34$), of whom 36 (67 %) were rapid cyclers, randomized them to receive divalproex ER (1,000–2,000 mg/day, serum levels 50–100 mg/ml; $N=26$) or placebo ($N=28$). Divalproex treatment produced statistically significant improvement in MADRS scores compared with placebo from week 1 onward, but this concerned only BD-I patients (−16 vs. −2). The divalproex ER group had significantly higher response (38.5 % vs. 10.7 %) and remission rates (23.1 % vs. 10.7 %). Response and remission appeared at day 38. Treatment effect concerned only BD-I patients. The dropout rate was similar between the two groups (50 % vs. 46.4 %), numerically higher for the divalproex ER group because of adverse events (7.7 % vs. 0 %)

and similar because of lack of efficacy (26.9 % vs. 28.6 %). The most common adverse events related with divalproex ER treatment were nausea, increased appetite, diarrhoea, dry mouth and cramps (Muzina et al. 2010).

A fourth study (Sachs et al. 2001) is not published and can be assessed only through two meta-analyses papers (Bond et al. 2010; Smith et al. 2010). This was an 8-week small study on 43 patients with BD-I ($N=24$) or BD-II ($N=19$), of whom 13 (29 %) were rapid cyclers. These patients were randomized to receive divalproex ER (titrated up to achieve serum levels of 45–95 μg/ml, $N=21$) or placebo ($N=22$). The two groups were similar concerning the improvement in MADRS scores (−9.7 vs. −8.1). The divalproex ER group had significantly higher response (42.9 % vs. 27.3 %) and remission rates (66.6 % vs. 45.5 %). The overall dropout rate was similar between the two groups (30.4 % vs. 36.4 %) and numerically higher for the placebo group because of adverse events (0 % vs. 9.1 %). The authors reported no difference in adverse events between the treatment groups.

Taken together the above, it seems that there are some (though somewhat inconsistent and not sufficient) data, coming from small trials supporting the efficacy of valproate in bipolar depression especially in BD-I patients and on the core symptoms of depression. There is possibly some efficacy against concomitant anxiety and in rapid cycling patients.

16.2.2.1.3 Carbamazepine

Although carbamazepine is considered to be one of the traditional 'mood stabilizers', and a cornerstone for the treatment strategy for many clinicians worldwide, there are only two studies. The first is an old positive small withdrawal study concerning its efficacy against bipolar depression. These authors evaluated carbamazepine (600–1,600 mg/day at blood levels of 8–12 μg/ml) on 13 bipolar depressed patients and reported that 5 of them (38.5 %) had a good to marked response. Three manifested a relapse when placebo substituted carbamazepine. Dizziness, ataxia, clumsiness, drowsiness, slurred speech and diplopia were the most frequent carbamazepine-related adverse events (Ballenger and Post 1980). The second was a 12-week double-blind, randomized, placebo-controlled study from China in 124 patients with acute bipolar depression which were randomized to carbamazepine (300–800 mg/day; $N=49$) vs. carbamazepine plus the herbal Free and Easy Wanderer Plus (FEWP; 36 g/day; $N=50$) vs. placebo ($N=25$). At endpoint patients under carbamazepine plus FEWP showed a significantly greater improvement on HAM-D score vs. both carbamazepine monotherapy and placebo, and the improvement was present already at week 4 (−13.5 vs. −16 vs. −10.6). A similar picture was there concerning the MADRS results. Carbamazepine monotherapy was similar with placebo in terms of HAM-D, and MADRS total score change from baseline and superior to placebo in terms of CGI change. In terms of response rates, carbamazepine plus FEWP was superior to carbamazepine alone, and both were superior to placebo (63.88 % vs. 84.8 % vs. 34.8 %, $p<0.001$). There was a similar dropout rate between the two carbamazepine groups and lower in comparison to placebo (26.5 % vs. 20 % vs. 40 %), and this was also true concerning dropout because of lack of efficacy (6.1 % vs. 6 % vs. 24 %). Depressed and manic patients were pooled for the

analysis of adverse events, and the adverse events occurring in over 5 % of the patients in any treatment group were dizziness, laboratory testing abnormality, skin rash, headache, fatigue, blurred vision, somnolence and nausea. Compared to carbamazepine monotherapy, patients in the combination therapy had a lesser incidence of dizziness (18.2 % vs. 7.9 %; $p=0.069$) and fatigue (9.1 % vs. 1.1 %; $p=0.038$). No difference in the incidence of other adverse events was found between the combination therapy and CBZ monotherapy. This study does not support the use of carbamazepine monotherapy against bipolar depression, but it leaves significant doubt (Zhang et al. 2007).

16.2.2.1.4 Lamotrigine

There are five trials which investigate the efficacy and safety of lamotrigine in the treatment of acute bipolar depression (SCA100223/NCT00274677, SCA30924/NCT00056277, SCA40910, SCAA2010 and SCAB2001). One included BD-II patients alone and one a mixed population of BD-I and BD-II patients. All were negative concerning the primary outcome. They showed some benefit on some of the secondary outcomes (Goldsmith et al. 2003; Calabrese et al. 2008).

In one of these studies, 195 outpatients with BD-I depression received fixed dosages of lamotrigine (50 mg/day; $N=66$ or 200 mg/day; $N=63$) or placebo ($N=66$) for 7 weeks. At endpoint there was no difference between groups in terms of change in HAM-D or MADRS scores, but there was a significant improvement for the 200 mg lamotrigine group in several secondary outcomes, and these improvements were seen as early as week 3. The response rate for lamotrigine 200 mg was 51 %, and it was higher than the reported 26 % for placebo. There was no difference in the overall dropout rate between the three groups (35 % vs. 29 % vs. 29 %), in the dropout rate because of adverse events (18 % vs. 16 % vs. 15 %) or because of lack of efficacy (0 % vs. 2 % vs. 3 %). The adverse events and other safety results were similar across treatment groups, with the exception of a higher rate of headache in the lamotrigine groups (Calabrese et al. 1999). In the other studies a flexible dose of 100–400 mg daily was used in one of them and a fixed dose of 200 mg/day in the three others. The trial duration for these studies varied from 7 to 10 weeks. In all of them lamotrigine was well tolerated but did not differ significantly from placebo at endpoint on the primary outcomes (HAM-D or MADRS), and seldom it differed on secondary outcomes (Calabrese et al. 2008). Finally, a small double-blind, randomized study with crossover series of three 6-week monotherapy evaluations compared lamotrigine (500 mg/day) vs. gabapentin (4,800 mg/day) vs. placebo in a mixed unipolar–bipolar population of 31 refractory depressed patients. The response rate according to CGI improvement was 52 % vs. 26 % vs. 23 %; $p=0.031$ (Frye et al. 2000).

Overall the data are negative concerning the efficacy of lamotrigine in bipolar depression although the presence of a weak signal cannot be ruled out.

16.2.2.1.5 Antidepressants

In spite of the fact that antidepressants have an established efficacy against unipolar depression, and this defines them as a class of drugs which includes different kinds

of molecules, such a 'class effect' is not present also for bipolar depression (Fountoulakis et al. 2011a). Although the data are problematic, the use of antidepressants is neither encouraged nor prohibited by all treatment algorithms which, however, consistently advise the concomitant use of an antimanic agent. Older placebo-controlled studies were mostly positive but difficult to judge on the basis of modern criteria and needs.

The first was a 6-week study on 59 refractory anergically depressed patients which were randomly assigned to tranylcypromine vs. placebo. At endpoint tranylcypromine was superior to placebo, and the effect was evident since week 1. The authors suggest that these results support the efficacy of tranylcypromine against bipolar depression since anergic depression most typically occurs in primary bipolar and in pseudounipolar affective illnesses (Himmelhoch et al. 1982).

However the first trial was properly conducted, and investigating the acute phase of bipolar depression took part only in 1989. It was a 6-week, double-blind study on 89 patients and compared fluoxetine (20–80 mg/day; $N=30$, of which 11 were receiving also lithium), imipramine (75–300 mg/day; $N=30$, which 5 were receiving also lithium) and placebo ($N=29$, which 6 were receiving also lithium) with bipolar depression. At endpoint there was a significant change in both treatment arms in comparison with placebo in terms of HAM-D score change (−13.9 vs. −9.7 vs. −3.9), and the response rate was 86 % for fluoxetine vs. 57 % for imipramine and 38 % for placebo. Fewer patients under fluoxetine dropped out (43 % vs. 53 % vs. 66 %), and this was also true because of lack of efficacy (7 % vs. 7 % vs. 38 %) and adverse events (7 % vs. 30 % vs. 10 %). The most frequent adverse events were insomnia, nervousness and excessive sweating for fluoxetine and dry mouth for imipramine. The interpretation of the results of this study is complicated by the concomitant use of lithium, especially in the fluoxetine group. Half of the patients on fluoxetine were receiving 80 mg daily, while 65 % under imipramine were receiving 150–300 mg daily (Cohn et al. 1989).

Another 8-week study on 34 depressed patients (32 BP-I and 2 BP-II) utilized fluoxetine monotherapy (10–60 mg/day; $N=8$) vs. olanzapine monotherapy (5–20 mg/day; $N=8$) vs. OFC, that is, olanzapine–fluoxetine combination (10–40 mg/day fluoxetine plus 2.5–15 mg/day olanzapine; $N=9$) and vs. placebo ($N=9$). There were significant reductions over time in mean HAM-D and MADRS ratings for all treatment groups (including the placebo group), but no difference between them. Interestingly, while there was no significant increase in YMRS scores over time in any treatment group, there was a significant reduction in the mean YMRS score in the fluoxetine group ($p=0.008$). This study was underpowered to detect any treatment effect (Amsterdam and Shults 2005a).

A small placebo-controlled crossover study lasting 9 months (on 10 BD-II depressed patients without any previous treatment with any antidepressant, antipsychotic or mood stabilizer drug) suggested that escitalopram (10 mg/day) might be better than placebo as monotherapy for depression. The results suggested that treatment with escitalopram led to a significant improvement in depression severity, lower percentage of days depressed or high and lower percentage of days impaired, in comparison with placebo. There was no indication that escitalopram led to a

worsening of illness course. Interestingly there was some signal that escitalopram was beneficial even concerning hypomania (Parker et al. 2006).

The only properly conducted study on a sample of adequate size was an international trial on 740 patients with bipolar depression (478 BD-I and 262 BD-II) which randomized them to receive quetiapine 300 mg/day ($N=245$), quetiapine 600 mg/day ($N=247$), paroxetine 20 mg/day ($N=122$) or placebo ($N=126$) for 8 weeks. The results suggested that both quetiapine groups demonstrated statistically significant improvement in the MADRS score vs. placebo at endpoint, but paroxetine did not (−16.9 vs. −16 vs. −11.9). Also, both quetiapine groups but not the paroxetine group manifested significantly higher response rates (66.8 % vs. 67.2 % vs. 51.1 % vs. 52.9 %); however, only the 600 mg/day quetiapine group manifested a significantly higher remission rate in comparison to placebo (64.6 % vs. 68.5 % vs. 56.8 % vs. 55.4 %). The overall dropout rate was similar in the four groups (34.7 % vs. 35.6 % vs. 37.7 % vs. 39.7 %), and it was numerically higher in the quetiapine and paroxetine groups due to adverse events (8.6 % vs. 12.1 % vs. 12.3 % vs. 7.9 %) and lower in both the quetiapine groups because of lack of efficacy (1.2 % vs. 2 % vs. 4.1 % vs. 4.8 %). Both quetiapine dosages and paroxetine produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline. Paroxetine had no significant effect on any MADRS item. A sub-analysis suggested that quetiapine was efficacious both in BD-I and in BD-II patients, while paroxetine was not efficacious in any subgroup of patients, not even in non-rapid cycling. The incidence of treatment-emergent mania/hypomania was numerically lower in the quetiapine groups compared with paroxetine and placebo (2.1 % vs. 4.1 % vs. 10.7 % vs. 8.9 %). The most frequent adverse events were dry mouth, sedation, headache, insomnia and nausea with paroxetine treatment (McElroy et al. 2010c).

16.2.2.1.6 Olanzapine

As mentioned above, an 8-week study on 34 bipolar depressed patients which utilized olanzapine monotherapy vs. fluoxetine monotherapy vs. OFC and vs. placebo was underpowered and negative (Amsterdam and Shults 2005a). Also another international 8-week trial (also mentioned above in detail) on 833 BD-I depressed patients which utilized olanzapine vs. OFC or placebo reported a superiority of both treatment groups in comparison to placebo in terms of MADRS score reduction as well as a longer time to treatment discontinuation. However, the analysis of individual MADRS items suggested that the OFC had an effect on the core symptoms of depression, while this was not the case for olanzapine monotherapy (Tohen et al. 2003c). It is widely accepted that when attempting to demonstrate a purely antidepressive effect, the total HAM-D or MADRS scores are not appropriate; instead subscales which include only the 'core items' of depression should be used, like the HAM-D depression factor (Bech 2001; Lecrubier and Bech 2007). To answer this question, another trial was conducted, on 514 patients with bipolar depression which were allocated to receive olanzapine (5–20 mg/day, $N=343$) or placebo ($N=171$) for 6 weeks. The results suggested that olanzapine demonstrated a significantly greater improvement on the MADRS (−13.8 vs. −11.67; $p=0.018$), the HAM-D and the YMRS scores. There was significantly higher response (52.5 % vs.

43.3 %; $p=0.049$) and remission rates (38.5 % vs. 29.2 %; $p=0.038$) for the olanzapine group in comparison to placebo. The response was evident since week 2. The analysis of individual MADRS items and the MADRS-6 subscale did not show an effect of olanzapine on the 'core' of depressive symptoms according to LOCF analysis, but on the contrary MMRM analysis showed a significant effect. The overall dropout rate was similar in the two groups (22.2 % vs. 28.7 %), and this was also true concerning dropout because of adverse events (8.7 % vs. 7.6 %) but not because of lack of efficacy (1.7 % vs. 7.6 %). Olanzapine caused significantly greater mean increases in weight, fasting cholesterol and triglycerides ($p<0.01$), and significantly more patients gained at least 7 % in body weight ($p<0.001$) (Tohen et al. 2012).

16.2.2.1.7 Quetiapine

The first trial on quetiapine in bipolar depression included 542 outpatients (BD-I, $N=360$; BD-II, $N=182$; 20 % rapid cycling) which were randomly assigned to 8 weeks of quetiapine (300 mg/day; $N=181$ or 600 mg/day; $N=180$) or placebo ($N=181$). Both quetiapine groups demonstrated statistically significant improvement in the MADRS score vs. placebo at endpoint (−16.4 vs. −16.7 vs. −10.3; $p<0.001$), and this was evident since week 1. The response rate was in favour of the quetiapine groups (57.6 % vs. 58.2 % vs. 36.1 %; $p<0.001$) and so was the remission rate (52.9 % in the quetiapine groups vs. 28.4 % for placebo; $p<0.001$). The overall dropout rate was similar in the three groups (33.3 % vs. 45.5 % vs. 40.9 %), numerically higher in the quetiapine groups due to adverse events (16 % vs. 26.1 % vs. 8.8 %) and lower because of lack of efficacy (2.2 % vs. 1.7 % vs. 13.3 %). Both quetiapine dosages produced a significant improvement in anxiety in terms of change of HAM-A scale from baseline. Both quetiapine dosages improved the core symptoms of depression; however, sub-analysis suggested that quetiapine was efficacious only in BD-I and not in BD-II patients but both in rapid and non-rapid cycling patients. Treatment-emergent mania rates were low and similar for all groups (3.2 % vs. 3.9 %). The most common quetiapine related adverse events were dry mouth, somnolence, dizziness and sedation (Calabrese et al. 2005a). A second study included 509 bipolar depressed outpatients (BD-I, $N=338$; BD-II, $N=171$; 30 % rapid cycling) which were randomly assigned to 8 weeks of quetiapine (300 mg/day; $N=172$ or 600 mg/day; $N=169$) or placebo ($N=162$). Both quetiapine groups demonstrated statistically significant improvement in the MADRS score vs. placebo at endpoint (−16.9 vs. −16 vs. −11.9; $p<0.001$), and this was evident since week 1. The response rate was in favour of the quetiapine groups (60 % vs. 58.3 % vs. 44.7 %; $p<0.05$) and so was the remission rates (51.6 % vs. 52.35 vs. 37.3 %, $p<0.05$). The overall dropout rate was similar in the three groups (41.3 % vs. 46.7 % vs. 34.5 %), numerically higher in the quetiapine groups due to adverse events (8.1 % vs. 11.2 % vs. 1.2 %) and lower because of and lack of efficacy (1.7 % vs. 2.9 % vs. 7.7 %). Both quetiapine dosages produced a significant improvement in anxiety in terms of change of HAM-A scale. Both quetiapine dosages improved the core symptoms of depression, and sub-analysis suggested that quetiapine was efficacious both in BD-I and in BD-II patients and also in rapid and non-rapid cycling patients. Treatment-emergent mania rates were low and similar for all

groups (2–4 % vs. 7 %). The most common quetiapine-related adverse events were dry mouth, somnolence, dizziness, sedation and constipation (Thase et al. 2006). A third international study on 740 patients with bipolar depression (478 BD-I and 262 BD-II) randomized them to receive quetiapine 300 mg/day ($N=245$), quetiapine 600 mg/day ($N=247$), paroxetine 20 mg/day ($N=122$) or placebo ($N=126$) for 8 weeks. Both quetiapine groups demonstrated statistically significant improvement in the MADRS score vs. placebo at endpoint, but paroxetine did not (−16.9 vs. −16 vs. −11.9). The improvement was evident since week 2. Both quetiapine groups but not the paroxetine group manifested significantly higher response rates in comparison to placebo (66.8 % vs. 67.2 % vs. 51.1 % vs. 52.9 %); however, only the 600 mg/day quetiapine group manifested a significantly higher remission rate (64.6 % vs. 68.5 % vs. 56.8 % vs. 55.4 %). The overall dropout rate was similar in the four groups (34.7 % vs. 35.6 % vs. 37.7 % vs. 39.7 %), numerically higher in the quetiapine and paroxetine groups due to adverse events (8.6 % vs. 12.1 % vs. 12.3 % vs. 7.9 %) and lower in the quetiapine groups because of lack of efficacy (1.2 % vs. 2 % vs. 4.1 % vs. 4.8 %). Both quetiapine dosages and paroxetine produced a significant improvement in anxiety in terms of change of HAM-A scale from baseline. Quetiapine 600 mg/day improved the core symptoms of depression, while this was equivocal for the 300 mg/day dosage. Paroxetine had no significant effect on any MADRS item. A sub-analysis suggested that quetiapine was efficacious both in BD-I and in BD-II patients, while paroxetine was not efficacious in any subgroup of patients, not even in non-rapid cycling. The incidence of treatment-emergent mania/hypomania was numerically lower with quetiapine compared with paroxetine and placebo (2.1 % vs. 4.1 % vs. 10.7 % vs. 8.9 %). The most frequent adverse events with both dosages of quetiapine treatment were dry mouth, somnolence, sedation and dizziness (McElroy et al. 2010c). Another 8-week study in 802 bipolar depressive patients (499 BD-I, 303 BD-II) investigated the efficacy and tolerability of quetiapine (300 mg/day; $N=265$ or 600 mg/day; $N=268$) vs. lithium (600–1,800 mg/day; $N=136$) and vs. placebo ($N=133$). The change in the mean MADRS total score at endpoint (−15.4 vs. −16.1 vs. −13.6 vs. −11.8) was significant concerning both quetiapine groups ($p<0.001$) vs. placebo, but it was not significant for lithium ($p=0.123$). Quetiapine improved most of the MADRS individual items suggesting the presence of an effect on the core depressive symptoms. A similar picture emerged with the HAM-D and the HAM-A. At endpoint, the response rate (68.6 % vs. 69.6 % vs. 62.5 % vs. 55.8 %) was significant for the two quetiapine groups ($p<0.05$ and <0.01) but not for lithium ($p=0.279$) in comparison to placebo and so were the remission rates (69.8 % vs. 70.3 % vs. 62.5 % vs. 55.0 %). The overall dropout rate in the quetiapine groups was similar to placebo but numerically higher of the dropout of the lithium group (24.5 % vs. 23.5 % vs. 14.4 % vs. 27.8 %), and this was in part due to a lower dropout rate in the lithium group because of adverse events (9.8 % vs. 13.1 % vs. 5.1 % vs. 8.3 %). The 600 mg quetiapine group had the lowest rate of dropout rate due to lack of efficacy (4.2 % vs. 0.7 % vs. 4.2 % vs. 5.3 %). The most common adverse events for both quetiapine groups were somnolence, dry mouth and dizziness. Quetiapine was significantly effective in BD-I but not in BD-II patients. It is unclear whether quetiapine or lithium was effective in

rapid cycling patients although there is some signal for lithium (Young et al. 2010). Finally, another study utilized 277 bipolar depressed outpatients (80 % BD-I; 27.4 % rapid cycling) which were randomly assigned to 8 weeks of quetiapine XR (300 mg/day, $N=139$) or placebo ($N=138$). The quetiapine XR group demonstrated statistically significant improvement in the MADRS score vs. placebo at endpoint (−17.4 vs. −11.9; $p<0.001$). The response rate was in favour of the quetiapine XR group (65.4 % vs. 43.1 %; $p<0.001$), and this was evident since week 2. Also significantly different was the remission rate (54.1 % vs. 39.4 %, $p=0.02$). The overall dropout rate was similar in the two groups (37.4 % vs. 30.4 %), numerically higher in the quetiapine XR group due to adverse events (12.2 % vs. 1.4 %) and lower because of and lack of efficacy (1.4 % vs. 7.2 %). Quetiapine XR improved the core symptoms of depression, and MMRM sub-analysis suggested that quetiapine XR was efficacious both in BD-I and in BD-II patients and also in rapid and non-rapid cycling patients. Treatment-emergent mania rates were low and similar in the two groups (4.4 % vs. 6.4 %). The most common quetiapine XR-related adverse events were dry mouth, somnolence, sedation and increased appetite (Suppes et al. 2010).

Overall, in five studies, all of whom were positive, quetiapine IR or XR is reported to be efficacious at dosages of 300 and 600 mg/day and produced response and remission rates approximately 20 % higher than placebo. It is important that quetiapine had a similar efficacy in BD-I and BD-II patients as well as in rapid cycling, and it significantly improved all the MADRS items corresponding to the core symptoms of depression and also improved concomitant anxiety.

16.2.2.1.8 Aripiprazole

Two identically designed, 8-week, multicentre, randomized, double-blind, placebo-controlled studies (CN138-096 and CN138-146) to evaluate the efficacy and safety of aripiprazole monotherapy in depressed BD-I outpatients without psychotic features were both negative for aripiprazole. Patients were randomized to receive aripiprazole (5–30 mg/day; $N=186$ and $N=187$) or placebo ($N=188$ and $N=188$). In both studies, although statistically significant differences were observed concerning the change in the MADRS score during weeks 1–6, aripiprazole did not achieve statistical significance vs. placebo at endpoint in either study (−11.9 and −12.3 vs. −10.6 and −11.5). The dropout rate was higher in the aripiprazole group in comparison to placebo (46.8 % and 41.2 % vs. 35.1 % and 29.8 %), and this was also the case due to adverse events (16.7 % and 10.2 % vs. 7.4 % and 5.3 %) but not because of lack of efficacy (3.2 % and 5.3 % vs. 8.5 % and 5.9 %). Treatment-emergent mania was similar in the two groups (3.9 % and 2.2 % vs. 2.2 % and 1.1 %). Treatment with aripiprazole was associated with a higher incidence of akathisia, insomnia, nausea, fatigue, restlessness and dry mouth vs. placebo (Thase et al. 2008). It has been argued that the failure of these two trials was due to the 'catching up' of the placebo group after week 6 rather than because of a lack of efficacy of aripiprazole. The fact is that at endpoint the placebo response in terms of MADRS score change in the aripiprazole studies (−10.6 and −11.5) is similar to what was observed also in the quetiapine studies (from −10.3 to −11.9), while the aripiprazole response (−11.9 and −12.3) is clearly lower to the response observed with quetiapine (from −15.4 to −17.4).

16.2.2.1.9 Ziprasidone

There are two negative unpublished trials concerning ziprasidone (Lombardo et al. 2012). The first was a 6-week, multicentre US study which utilized a fixed-flexible dose and evaluated the efficacy and safety of ziprasidone in 504 depressed outpatients with BD-I. Patients were randomized to ziprasidone (40–80 mg/day; $N=165$ or 120–160 mg/day; $N=171$) or placebo ($N=168$). The results suggested no difference between study groups in terms of change in MADRS score from baseline (–14.8 vs. −13.8 vs. −13.3) or in the response rates (53 % vs. 46 % vs. 49 %). The dropout rate was similar between groups (35.8 % vs. 43 % vs. 32.8 %), numerically higher for the ziprasidone groups due to adverse events (9.78 % vs. 14 % vs. 5.4 %) and also due to lack of efficacy (4.2 % vs. 4.1 % vs. 1.8 %) (NCT00141271). The second was also a 6-week, multicentre US study which again utilized a fixed-flexible dose and evaluated the efficacy and safety of ziprasidone in 392 depressed outpatients with BD-I. Patients were randomized to ziprasidone (40–160 mg/day; $N=192$) or placebo ($N=200$). Again the results suggested no difference between study groups in terms of change in MADRS score (−14.9 vs. −13.2) from baseline or response rates (53 % vs. 51 %). The dropout rate was similar between groups (38 % vs. 31 %) (NCT00282464).

16.2.2.1.10 Lurasidone

One 6-week trial on 335 bipolar depressed patients without psychotic features which were randomly assigned to receive lurasidone (20–60 mg/day; $N=166$ or 80–120 mg/day; $N=169$) or placebo ($N=170$) reported that both lurasidone dosages significantly reduced the MADRS total scores at endpoint (−15.4 and −15.4 vs. −10.7). Lurasidone had an effect on the core symptoms of depression. Both lurasidone groups also experienced significant improvements compared with placebo in anxiety symptoms and in patient-reported measures of quality of life and functional impairment. Discontinuation rates were similar in the three groups (25.9 % vs. 26.6 % vs. 25.3 %), and this was true also due to adverse events (6.6 % vs. 5.9 % vs. 6.5 %). Dropout because of lack of efficacy was lower in the 80–120 mg/day lurasidone group (7.2 % vs. 3 % vs. 7.6 %). More patients in the lurasidone groups were experiencing response (53 % vs. 51 % vs. 30 %; $p<0.001$) and remission (42 % vs. 40 % vs. 25 %; $p<0.01$) at endpoint. The most frequent adverse events associated with lurasidone were nausea, headache, akathisia and somnolence. Minimal changes in weight, lipids and measures of glycaemic control were observed with lurasidone (Loebel et al. 2013). Although this was a 6-week study and given the negative findings at endpoint (week 8) for aripiprazole while the data was positive at week 6, one should be cautions concerning the interpretation of the lurasidone data. However the magnitude of improvement and the absolute values of lurasidone- and placebo-induced change in the MADRS score argue in favour of lurasidone.

16.2.2.1.11 Other Agents and Therapeutic Modalities

There is a small number of early studies on very small samples (Jimerson et al. 1980; Osman et al. 1989; Kastin et al. 1972). A prospective, randomized controlled, multicentre 6-week trial involving 132 bipolar depressive patients resistant to

treatment compared ECT vs. algorithm-based pharmacological treatment as usual has been announced (Kessler et al. 2010). No results have been publicized until now. One uncontrolled trial on 220 patients suggested that bipolar depressives respond to ECT in a similar magnitude unipolar depressives do. The study included 170 unipolar and 50 bipolar depressive patients. The response and remission rates and numbers of ECT for both groups were equivalent (Bailine et al. 2010). However another uncontrolled study suggested that BD-I depressed patients respond less well in comparison to BD-II, and in turn BD-II respond less well in comparison to unipolar depressives (Medda et al. 2009).

There is one study on repetitive transcranial magnetic stimulation (rTMS) which included 23 depressed BD patients (12 BP-I, 9 BP-II and 2 BP-I in a mixed state). Patients were randomly assigned to daily left prefrontal rTMS (5 Hz, 110 % motor threshold, 8 s on, 22 s off, over 20 min) vs. placebo each weekday morning for 2 weeks. The results suggested that the two treatment groups were similar in terms of response and mean HAM-D change from baseline over the 2 weeks (Nahas et al. 2003).

16.2.2.1.12 Conclusion of Monotherapy Trials for the Treatment of Acute Bipolar Depression

The data are clearly negative for lithium even at high serum concentration levels and also for lamotrigine, while there are some (though somewhat inconsistent and not sufficient) positive data concerning valproate. They are equivocal for carbamazepine. Antidepressants as a class do not have an established efficacy against bipolar depression. Older placebo-controlled studies were somewhat positive but difficult to judge on the basis of modern criteria and needs. There are some inconclusive data concerning escitalopram and fluoxetine monotherapy, while the data are clearly negative for paroxetine. Quetiapine and lurasidone have positive data with a clear beneficial effect on the core depressive symptoms, while the evidence is negative concerning aripiprazole and ziprasidone. Olanzapine monotherapy might work against bipolar depression but probably without an effect on the 'core' of depressive symptoms.

Quetiapine, lurasidone and maybe valproate have some positive efficacy against concomitant anxiety as well. This is true also for paroxetine which seems to improve concomitant anxiety independently of its lack of effect on depression.

16.2.2.2 Comparison of Treatment Options

Since only a limited number of options for the treatment of bipolar depression exist, comparison studies are limited, and often they compare agents with unproven efficacy.

Some early studies were too small and with problems in methodology (Kessell and Holt 1975; Coppen et al. 1972; Aberg-Wistedt 1982).

The first properly conducted comparison trial was a 6-week, double-blind study on 89 patients with bipolar depression and compared fluoxetine (20–80 mg/day; $N=30$, 11 receiving also lithium), imipramine (75–300 mg/day; $N=30$, 5 receiving also lithium) and placebo ($N=29$, 6 receiving also lithium). At endpoint there was a significant

change in both treatment arms in comparison to placebo in terms of HAM-D score change from baseline (−13.9 vs. −9.7 vs. −3.9), and the response rate was 86 % for fluoxetine vs. 57 % for imipramine and 38 % for placebo. Fewer patients under fluoxetine dropped out (43 % vs. 53 % vs. 66 %), and this was also true because of lack of efficacy (7 % vs. 7 % vs. 38 %) and adverse events (7 % vs. 30 % vs. 10 %). The most frequent adverse events were insomnia, nervousness and excessive sweating for fluoxetine and dry mouth for imipramine. The interpretation of the results of this study is complicated by the concomitant use of lithium especially in the fluoxetine group. Half of the patients on fluoxetine were receiving 80 mg daily, while 65 % under imipramine were receiving 150–300 mg daily (Cohn et al. 1989).

A 4-week multicentre trial compared moclobemide (400–600 mg/day; $N=18$) vs. imipramine (133–200 mg/day; $N=15$) in 33 patients (some receiving also lithium) and reported similar efficacy in both treatment arms with response rates of 53 and 60 %, respectively. Dropout rates were comparable. The number of patients presenting with adverse events, as well as the total number of adverse events, was greater with imipramine (Baumhackl et al. 1989). A small 6-week study on 56 BD-I ($N=24$) and BD-II ($N=32$) (rapid cycling excluded) patients suffering from 'anergic depression' compared the efficacy of tranylcypromine (30–60 mg/day; $N=28$) with that of imipramine (150–300 mg/day; $N=28$). The results suggested that tranylcypromine produced statistically significant superior outcome in terms of greater symptomatic improvement. More patients under tranylcypromine who completed the study responded (81 % vs. 48 %; $p=0.02$), while fewer dropped out (7 % vs. 25 %; $p=0.03$), and the proportion of patients which switched to mania/hypomania was numerically higher in the imipramine group (12 % vs. 24 %). The authors proposed that tranylcypromine had a specific effect on anergia and reversed neurovegetative symptoms. BD-I and BD-II patients had comparable outcomes, but BD-I patients had a significantly greater risk of treatment-emergent mood swings (38 % vs. 13 %; $p=0.03$) (Himmelhoch et al. 1991). A crossover study of nonresponders of the previous study reported that 9 out of 12 patients which were crossed over from imipramine to tranylcypromine responded, but in comparison only 1 out of 4 patients which were switched from tranylcypromine to imipramine responded (Thase et al. 1992).

Another small 6-week study included 16 BD-I depressed patients that were randomly assigned in this double-blind outpatient study to receive either idazoxan (up to 240 mg/day; $N=7$) or bupropion (up to 450 mg/day; $N=9$). The small study sample did not allow the detection of any differences between treatment arms (Grossman et al. 1999). A study compared 15 depressed women with BP-II with 17 women with unipolar depression which were randomized to receive once vs. twice daily venlafaxine monotherapy up to 225 mg for 6 weeks. The results suggested a similar efficacy for venlafaxine in the two diagnostic groups without any episodes of drug-induced hypomania or rapid cycling (Amsterdam and Garcia-Espana 2000).

An 8-week international multicentre study in 156 bipolar depressed patients randomized them to moclobemide (450–750 mg/day; $N=81$) or imipramine (150–250 mg/day; $N=75$). There were no statistically significant differences between the two groups on any efficacy measures or on the dropout rate for any reason. Anticholinergic side effects were three times more common with imipramine than

moclobemide, and weight gain was also greater on imipramine. More patients under imipramine switched to mania (3.7 % vs. 11 %) (Silverstone 2001).

As already mentioned above, olanzapine and the OFC were compared vs. placebo in one international 8-week trial on 833 BD-I depressed patients (one-third rapid cycling). These patients were assigned to receive olanzapine (5–20 mg/day; $N=370$) or OFC (6 and 25, 6 and 50 or 12 and 50 mg/day, $N=86$) or placebo ($N=377$). Both treatment groups showed statistically significant improvement in depressive symptoms (MADRS score) vs. the placebo group (−15 vs. −18.5 vs. −11.9; $p<0.001$). The response rate was higher in the two treatment groups in comparison to placebo (39 % vs. 56.1 % vs. 30.4 %), and this was true also for remission rates (32.8 % vs. 48.8 % vs. 24.5 %). Treatment-emergent mania did not differ among groups (5.7 % vs. 6.4 % vs. 6.7 %). The overall dropout rate was in favour of the OFC (51.6 % vs. 36 % vs. 61.5 %), and this was also true concerning the dropout rate due to adverse events (9.2 % vs. 2.3 % vs. 5 %) and due to lack of efficacy (19.7 % vs. 9.3 % vs. 32.1 %). Also the time to discontinuation was significantly longer in the olanzapine and the OFC group. Conclusively the OFC was superior to olanzapine monotherapy, and both were superior to placebo in the treatment of acute bipolar depression. The OFC arm was relatively small (only 86 patients). The analysis of individual MADRS items suggested that the OFC had an effect on the core symptoms of depression, while this was not the case for olanzapine monotherapy (Tohen et al. 2003c). One 7-week trial compared OFC (6/25, 6/50, 12/25 or 12/50 mg/day; $N=205$) vs. lamotrigine (titrated to 150–200 mg/day; $N=205$) in 410 BD-I depressed patients (one-third rapid cyclers). The OFC-treated patients had significantly greater improvement than lamotrigine-treated patients in MADRS score change from baseline (−18.5 vs. −16.4; $p=0.02$). The response rates did not significantly differ between groups (68.8 % vs. 59.7 %; $p=0.073$) and neither did remission rates (56.4 % vs. 49.2 %; $p=0.16$). Time to response was significantly shorter for OFC-treated patients (17 vs. 23 days; $p=0.010$), but not time to remission or time to discontinuation. There was a significantly higher incidence of 'suicidal and self-injurious behaviour' adverse events in the lamotrigine group (0.5 % vs. 3.4 %; $p=0.037$). The dropout rate was similar between treatment groups (33.2 % vs. 34.6 %). Somnolence, increased appetite, dry mouth, sedation, weight gain and tremor occurred more frequently in the OFC group ($p<0.05$), and also weight and total cholesterol and triglyceride levels were significantly elevated in the OFC group ($p<0.001$) (Brown et al. 2006).

The single-blind 6-week comparison of paroxetine ($N=28$) vs. venlafaxine ($N=27$) in 55 bipolar depressed patients which were already receiving mood stabilizers reported no significant differences in either efficacy or safety between the two treatment groups. The change in the HAM-D total score from baseline (−6.9 vs. −9), the response (43 % vs. 48 %) and the remission rates (42 % vs. 43 %) were similar in the two groups. Also the dropout rate was similar (43 % vs. 50 %), but more patients under paroxetine dropped out because of lack of efficacy (7 % vs. 0 %), while more under venlafaxine dropped out because of switching to mania (3 % vs. 13 %). The adverse effect profile was similar between groups. There was no difference between BD-I and BD-II patients or between those taking lithium and

those taking anticonvulsants (Vieta et al. 2002). The relatively higher risk of treatment-emergent affective switches with venlafaxine compared to sertraline or bupropion has also been confirmed in an add-on trial (Post et al. 2006).

Overall the comparison data are sparse. They suggest that antidepressants are equal in efficacy but with a different adverse events profile. However the efficacy of antidepressants should be considered in combination with the negative monotherapy data. The frequent use of concomitant mood stabilizers as 'background' medication complicates the interpretation of results. The OFC is superior to olanzapine alone and to lamotrigine and with an effect on the core symptoms of depression. The comparison of paroxetine with venlafaxine suggests a higher switching risk for patients treated with venlafaxine.

16.2.2.3 Combination and Add-On Treatment

A summary of combination treatment data for the treatment of acute bipolar depression is shown in Table 16.5.

16.2.2.3.1 Combination Treatment

There are only three studies of proper methodology and size utilizing a combination treatment. The first was one international 8-week trial on 833 BD-I depressed patients (one-third rapid cycling) which were assigned to receive olanzapine (5–20 mg/day; $N=370$) or OFC (6 and 25, 6 and 50 or 12 and 50 mg/day, $N=86$) or placebo ($N=377$). Both treatment groups showed statistically significant improvement in the depressive symptoms (MADRS score) vs. the placebo group (−15 vs. −18.5 vs. −11.9; $p<0.001$). The response rate was higher in the two treatment groups in comparison to placebo (39 % vs. 56.1 % vs. 30.4 %), and this was true also for remission rates (32.8 % vs. 48.8 % vs. 24.5 %). Treatment-emergent mania did not differ among groups (5.7 % vs. 6.4 % vs. 6.7 %). The dropout rate was in favour of the OFC. This was true concerning the overall dropout rate (51.6 % vs. 36 % vs. 61.5 %), as well as dropout due to adverse events (9.2 % vs. 2.3 % vs. 5 %) and due to lack of efficacy (19.7 % vs. 9.3 % vs. 32.1 %). The time to discontinuation was significantly longer in the olanzapine and the OFC group. That study concluded that the OFC was superior to olanzapine monotherapy, and both were superior to placebo in the treatment of acute bipolar depression. The OFC arm was relatively small (only 86 patients), and this was one of the limitations of the study. Other limitations were that in comparison to placebo and olanzapine, the OFC arm had a lower number of inpatients, less frequent psychotic features, more rapid cycling (possibly higher rates of 'spontaneous remission') and lower number of centres. The analysis of individual MADRS items suggested that the OFC had an effect on the core symptoms of depression, while this was not the case for olanzapine monotherapy (Tohen et al. 2003c).

A second recent double-blind 26-week placebo-controlled study from the USA (STEP-BD) compared the adding of paroxetine (10–40 mg/day; $N=93$) or bupropion (150–375 mg/day; $N=86$) vs. placebo ($N=187$) on a mood stabilizer in 366 bipolar depressed patients (two-thirds BD-I, 29.4 % rapid cycling). The results suggested that the two antidepressant arms did not perform significantly better than placebo after 26 weeks of treatment in terms of recovery rates (23.5 % vs. 27.3 %)

or transient remission (17.9 % vs. 21.4 %). Switch rates were similar (10.1 % vs. 10.7 %) as was the dropout rate (34.1 % vs. 33.7 %) and adverse events (9.5 % vs. 7 %). Modest nonsignificant trends favouring the placebo group were observed across the secondary outcomes. There was no difference between BD-I and BD-II patients (Sachs et al. 2007).

The third was a 12-week double-blind, randomized, placebo-controlled study from China in 124 patients with acute bipolar depression which were randomized to carbamazepine (300–800 mg/day; $N=49$) vs. carbamazepine plus the herbal Free and Easy Wanderer Plus (FEWP; 36 g/day; $N=50$) vs. placebo ($N=25$). At endpoint patients under carbamazepine plus FEWP showed a significantly greater improvement on HAM-D score vs. both carbamazepine monotherapy and placebo, and the improvement was present already at week 4 (−13.5 vs. −16 vs. −10.6). A similar picture was there concerning the MADRS results. In terms of response rates, more patients in the carbamazepine plus FEWP responded both in comparison to carbamazepine monotherapy and in comparison to placebo (63.88 % vs. 84.8 % vs. 34.8 %, $p<0.001$). There was a similar dropout rate between the two carbamazepine groups and lower in comparison to placebo (26.5 % vs. 20 % vs. 40 %), and this was also true concerning the dropout because of lack of efficacy (6.1 % vs. 6 % vs. 24 %). Depressed and manic patients were pooled for the analysis of adverse events, and the adverse events occurring in over 5 % of the patients in any treatment group were dizziness, laboratory testing abnormality, skin rash, headache, fatigue, blurred vision, somnolence and nausea. Compared to carbamazepine monotherapy, patients in the combination therapy had a lesser incidence of dizziness (18.2 % vs. 7.9 %; $p=0.069$) and fatigue (9.1 % vs. 1.1 %; $p=0.038$). No difference in the incidence of other adverse events was found between the combination therapy and CBZ monotherapy. This study supports the use of carbamazepine plus FEWP against bipolar depression. The negative results concerning carbamazepine monotherapy, in combination with the possible dramatic reduction of carbamazepine levels when co-administered with FEWP, plus the unusually high response rate even in the placebo group and the unusually low dropout rate, make conclusions difficult (Zhang et al. 2007).

A small study in 21 patients with BD-II in an acute depressive phase on therapeutic levels of lithium or valproate was randomly assigned to treatment with pramipexole ($N=10$) or placebo ($n=11$) for 6 weeks. All subjects except for one in each group completed the study. There was a superiority of pramipexole in terms of response (60 % vs. 9 %; $p=0.02$). One subject on pramipexole and two on placebo developed hypomanic symptoms (Zarate et al. 2004). Another small study randomized 17 BD depressed patients to receive adjunctive inositol or placebo for 6 weeks on lithium or valproate. The results were numerically in favour of inositol in terms of response rates (44 % vs. 0 %; $p=0.053$) (Eden Evins et al. 2006).

16.2.2.3.2 Add-On Treatment

Add-On Treatment on Lithium

There are a few studies which investigate the efficacy and safety of adding various agents on top of ongoing lithium treatment which was proven inadequate either to treat the acute depressive episode or to prevent its development.

The first properly conducted trial took place only in 1993, and it was a 4-week trial in 30 BD outpatients on maintenance treatment with lithium, suffering from a major depressive recurrence. They were randomized to L-sulpiride (50–75 mg/day; $N=15$) or amitriptyline (50–75 mg/day; $N=15$). L-sulpiride showed equivalent antidepressant activity to amitriptyline at endpoint in terms of HAM-D score change from baseline and in terms of response rate (93 % vs. 86 %). The onset of action was faster in the L-sulpiride group. The adverse events rate was similar in the two groups. Two patients in the amitriptyline group dropped out, and one patient from each group switched to mania or hypomania. The lack of a placebo arm in this trial makes conclusions difficult (Bocchetta et al. 1993).

Another multicentre 10-week study in 117 BD depressed outpatients (rapid cyclers excluded) investigated paroxetine (20–50 mg/day; $N=35$) vs. imipramine (50–300 mg/day; $N=39$) vs. placebo ($N=43$) as add-on to lithium (at least 7 weeks of lithium treatment before entering the study). In addition to lithium monotherapy, patients may have received either carbamazepine or valproate (but not both) in combination with lithium for the control of manic symptoms. The authors stratified patients on the basis of trough serum lithium levels determined at the screening visit (cut-off 0.8 meq/l). At endpoint there was no difference in terms of HAM-D score change in the three groups (−10.2 vs. −11.1 vs. −8.6), and the authors reported that antidepressants were beneficial for patients with low (−10.4 vs. −10.7 vs. 5.8) but not for high levels of lithium. A similar picture was present concerning the response (45.5 % vs. 38.9 % vs. 34.9 %) and remission rates (56.0 % vs. 47.8 % vs. 53.8 %). Compared to imipramine, paroxetine resulted in a lower incidence of adverse events, most notably emergence of manic symptoms (Nemeroff et al. 2001). This particular study has been criticized concerning the way it presented the data and because it puts too much emphasis on a post hoc analysis of the subgroup of patients with low lithium levels (Amsterdam and McHenry 2012).

Another 8-week study from the Netherlands in 124 depressed outpatients with BD (two-thirds BD-I, without psychotic features, severe rapid cycling excluded, 12.9 % rapid cycling) reported that adding lamotrigine (titrated to 200 mg/day; $N=64$) to ongoing lithium treatment (serum levels 0.6–1.2 mmol/l) was better than placebo ($N=60$). At endpoint, the lamotrigine group manifested significantly greater mean change from baseline in the MADRS total score (−15.38 vs. −11.03; $p=0.024$). Also, lamotrigine was effective in the core symptoms of depression. Significantly more patients responded to lamotrigine than to placebo (51.6 % vs. 31.7 %, $p=0.030$). The overall dropout rate was similar in the two groups (18.7 % vs. 15 %), and this was also true because of lack of efficacy (3.1 % vs. 5 %) and adverse events (6.3 % vs. 3.3 %). Switch to mania or hypomania occurred more often in the lamotrigine group, but this was not significant (7.8 % vs. 3.3 %; $p=0.441$) (van der Loos et al. 2009). In the second phase of the previous study, paroxetine 20 mg was added to ongoing treatment in those who were nonresponders after 8 weeks of treatment. After an additional 8-week treatment, the improvement in the two groups (lamotrigine plus lithium plus paroxetine vs. lithium plus paroxetine) was similar, and the difference was not significant. The disappearance of the difference was not due to a further improvement in the group of patients treated previously with lithium plus lamotrigine but in an improvement in the lithium plus

placebo group. Thus, the conclusion from this complex series of studies could be that lithium plus paroxetine is effective at least in a subgroup of BD patients which were refractory to lithium monotherapy. Since lithium monotherapy is not efficacious in the treatment of bipolar depression (as shown above in the monotherapy section), it could be assumed (although not entirely supported by the data) that both lamotrigine and paroxetine are effective in the treatment of bipolar depression as add-on to ongoing lithium treatment (van der Loos et al. 2010). However a careful analysis of the results of this series of studies questions whether the therapeutic effect persists beyond week 12 (van der Loos et al. 2010, 2011).

Another 8-week trial on 52 incomplete responders (two-thirds female; 27 BD-I, 25 BD-II) utilized the adding of carbamazepine (600–1,200 mg/day; $N=26$) or oxcarbazepine (600–1,200 mg/day; $N=26$) during maintenance treatment with lithium. Although this trial was on patients in the 'maintenance' phase, the design and the results are more relevant to the acute depressive phase since the study sample included depressed patients. All patients completed the trial. Both groups improved with the addition of either drug, but those receiving oxcarbazepine improved significantly more on their MADRS (−6.1 vs. −12.2; $p<0.001$) and HAM-D scores at endpoint (Juruena et al. 2009).

Finally, a 6-week double-blind study investigated the efficacy and safety of antidepressant augmentation in 42 bipolar patients under lithium maintenance treatment who were suffering from a breakthrough episode of major depression. These patients were randomly assigned to receive paroxetine (20–40 mg/day; $N=19$) or amitriptyline (75–150 mg/day; $N=23$). At the end of the study, there was no difference between study groups in terms of HAM-D score change from baseline (–14.9 vs. −15.5 $p=0.798$) or in response, remission or dropout rates. No effect of lithium levels on antidepressant efficacy was found (Bauer et al. 1999; Pilhatsch et al. 2010).

Overall, the data suggest that in bipolar depressed patients who experience depression while under lithium treatment, it is appropriate to add lamotrigine or oxcarbazepine but not imipramine. The data on adding paroxetine are equivocal.

Add-On Treatment on Lithium or Valproate

A 6-week study in 27 depressed outpatients (9 men and 18 women) with bipolar disorder (BD-I, $N=11$; BD-II, $N=16$) without psychotic features, being treated with lithium or divalproex, tried to clarify the appropriate treatment strategy by comparing the addition of paroxetine ($N=11$) vs. a second mood stabilizer ($N=16$). Although there was a numerically greater improvement in the combined mood stabilizers group concerning the change in the HAM-D score (−14 vs. –9), this was not significant. There were significantly more dropouts in the combined mood stabilizers group (Young et al. 2000).

One of the most interesting recent trials was single centred and utilized a randomized, placebo-controlled, double-blind, crossover design. It included 18 refractory bipolar depressed patients (44 % BD-I) without psychotic features who were maintained at therapeutic levels of lithium or valproate. These patients received an intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days 2 weeks apart. The MADRS was applied at baseline and at 40, 80, 110 and 230 min and on days 1, 2, 3, 7, 10 and 14 post-infusion. The results suggested that

within 40 min, depressive symptoms significantly improved in the ketamine group in comparison to the placebo group (effect size $d=0.52$). The improvement remained significant through day 3. There was also a significant difference concerning the response rate (71 % vs. 6 %). One patient from each group developed manic symptoms. The most common adverse effect related to ketamine treatment was dissociative symptoms, only at the 40-min point (Diazgranados et al. 2010). A second small double-blind, randomized, crossover, placebo-controlled study on 15 refractory bipolar depressed patients (60 % BD-I, no rapid cycling during the past year) without psychotic features, maintained on therapeutic levels of lithium or valproate, randomized them to receive a single intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo with a protocol identical to that of the previous study. The results suggested again that within 40 min, depressive symptoms, as well as suicidal ideation, significantly improved in the ketamine group vs. placebo ($d=0.89$). The improvement remained significant through day 3. More patients in the ketamine group responded in comparison to placebo (79 % vs. 0 %) at some point during the trial. The most common side effect was dissociative symptoms, which occurred only at the 40-min time point. These results were similar to a previous study and replicated previous findings. In addition, this study reported an effect of ketamine on the suicidal ideation in these patients (Zarate et al. 2012).

The most recent international study was of 6-week duration in 348 BD-I depressed patients without psychotic features and investigated the efficacy of lurasidone (20–120 mg/day; $N=183$) vs. placebo ($N=165$) as adjunctive therapy on lithium or valproate. At endpoint, lurasidone was superior to placebo in terms of MADRS score reduction from baseline (−17.1 vs. −13.5; $p=0.005$). Significantly more patients in the lurasidone group were responders (57 % vs. 42 %; $p=0.005$), and significantly more achieved remission (50 % vs. 35 %; $p=0.008$) at endpoint. Adjunctive lurasidone had an effect on the core depressive symptoms, and the overall effect was unrelated to whether the patient was receiving lithium or valproate. Lurasidone exerted a significantly greater improvement in anxiety symptoms and in patient-reported measures of quality of life and functional impairment. The overall dropout rates were similar in the two groups (21.9 % vs. 17.6 %), and this was also true concerning the dropouts because of adverse events (6 % vs. 7.9 %) and lack of efficacy (4.9 % vs. 3 %). The most frequent adverse events related to lurasidone treatment were nausea, somnolence, tremor, akathisia and insomnia. Minimal changes in weight, lipids and measures of glycaemic control were observed during treatment with lurasidone (Loebel et al. 2014).

Overall the data suggest that in BD patients experiencing depression during treatment with lithium or valproate, it would be appropriate to add ketamine or lurasidone. Lurasidone also improves anxiety, and ketamine improves suicidality in these patients. Response to a single ketamine infusion appears within minutes and does not last more than 3 days.

Add-On Treatment on Lithium Plus Other Agents

A small placebo-controlled adjunctive study on 23 BD patients (rapid cycling excluded) of aripiprazole on lithium and citalopram was negative. Before randomization, patients had to be on a constant mood stabilizer treatment with lithium or

valproate for at least 1 week. After inclusion, all patients were openly treated with additional citalopram (20–40 mg/day) and with additional aripiprazole (10–30 mg/day; $N=12$) or placebo ($N=11$) for 6 weeks. At endpoint there was no significant difference between the two groups with respect to the HAM-D change or response or dropout rates. However the study was underpowered, and the study sample was too small to detect any differences (Quante et al. 2010).

Add-On Treatment on a Mood Stabilizer

A small 8-week trial on 15 bipolar depressed patients to assess efficacy and rate of treatment-emergent mood elevation in depressed BD patients when bupropion (358 ± 62 mg/day; $N=7$) or desipramine (140 ± 46 mg/day; $N=8$) was added to an ongoing therapeutic regimen of lithium, valproate or carbamazepine reported that there was no difference concerning the acute efficacy between the two drugs. The response rate was similar (63 % vs. 71 %). Switching to mania/hypomania was more frequent in the desipramine group (11 % vs. 50 %; $p=0.01$) (Sachs et al. 1994).

Sixty-four BD patients (one-third BD-II, almost half rapid cycling) with a breakthrough major depressive episode despite ongoing adequately dosed mood stabilizer medication were randomized in a double-blind manner to bupropion (up to 450 mg/day), sertraline (up to 200 mg/day) or venlafaxine (up to 375 mg/day) for 10 weeks. Nonresponders were re-randomized such that there were 95 acute treatment phases. The results suggested that 37 % of the acute treatment phases were associated with a much or very much improved rating in depression, and 14 % were associated with switches. No comparisons between agents were reported by this study (Post et al. 2001).

A 12-week small study on 30 BD nonpsychotic depressed patients who were receiving a stable dose of a mood stabilizer investigated the efficacy and safety of add-on risperidone (1–4 mg/day; $N=10$) vs. paroxetine (20–40 mg/day; $N=10$) vs. the combination of risperidone and paroxetine ($N=10$). There was no difference in the HAM-D score change between the three groups (–5.2 vs. −5.6 vs. −6.3), and this was true also concerning the MADRS score change. There was a significant improvement of the combination group in comparison to the paroxetine group in terms of YMRS score change, but the switch rate into mania or hypomania was very low, with only one patient in the paroxetine plus placebo condition experiencing mild hypomania. More patients in the risperidone groups dropped out in comparison to the paroxetine group (Shelton and Stahl 2004).

Another 10-week trial in 174 BD (26 % BD-II; 27 % rapid cycling) depressed patients (stratified for rapid cycling) examined the relative acute effects of bupropion (75–450 mg/day; $N=51$), sertraline (50–200 mg/day; $N=58$) and venlafaxine (37.5–375 mg/day; $N=65$) as adjuncts to ongoing mood stabilizers. The response (49 % vs. 53 % vs. 51 %) and the remission rate (41 % vs. 36 % vs. 34 %) were similar in the three groups, and the specific combination with lithium vs. other mood stabilizers did not alter the results. The dropout rate was numerically higher in the venlafaxine group (31 % vs. 41 % vs. 45 %), and this was also true for reasons of lack of efficacy or worsening of mood (29 % vs. 28 % vs. 38 %). There was a significantly increased risk of switches into hypomania or mania in the venlafaxine

group (10 % vs. 9 % vs. 29 %; $p=0.002$). This was true for rapid cycling (0 % vs. 8 % vs. 29 %; $p<0.01$) but not non-rapid cycling patients (7 % vs. 6 % vs. 12 %; $p=0.55$) (Post et al. 2006).

A 12-week pilot trial in 20 BD depressed patients (85 % females, 60 % BD-I, 20 % rapid cycling) without psychotic features investigated the addition of lamotrigine (50–200 mg/day; $N=10$) vs. citalopram (10–30 mg/day; $N=10$) on ongoing treatment with a mood stabilizer. At endpoint there was no difference between the treatment groups in the MADRS score change from baseline (−13.3 vs. −14.2; $p=0.78$). There was a numerical but not significant difference in both the response (45 % vs. 60 %) and the remission (35 % vs. 60 %) rates at endpoint in favour of citalopram. Switching to hypomania occurred in 10 % of patients in each group (Schaffer et al. 2006).

A 10-week trial with three treatment cycles on 174 bipolar depressed patients randomized them to receive bupropion, sertraline or venlafaxine on top of their ongoing mood stabilizer. Each cycle included shift to treatment with another one from the three antidepressants. Half of the patients responded at the endpoint of the first treatment cycle, but only a few additional responded during the subsequent treatment cycles (Altshuler et al. 2009).

The small 6-week study in 32 BD depressed patients (71.9 % BD-I, 21.9 % rapid cycling) compared levetiracetam (up to 2,500 mg/day; $N=17$) vs. placebo ($N=15$) as adjunctive treatment to their ongoing medication. There was no significant difference between the two treatment groups in terms of MADRS score change from baseline; however, there was a numerical superiority of the placebo group. Also significantly more patients in the placebo group remitted (0 % vs. 23 %; $p=0.02$). More patients in the levetiracetam group dropped out (41.2 % vs. 26.6 %). This is the only study showing some kind of superiority of placebo vs. the active drug, thus suggesting that levetiracetam might in fact worsen depression in BD patients (Saricicek et al. 2010).

Finally, an international study included 298 depressed BD-I patients without psychotic features and assessed the efficacy and safety of ziprasidone (40–160 mg/day; $N=147$) vs. placebo ($N=147$) as adjunct therapy to an ongoing treatment with lithium, lamotrigine or valproate. At endpoint there was no difference between groups in terms of MADRS total score change for baseline (−13.2 vs. −12.9; $p=0.792$). More patients under ziprasidone dropped out (40.1 % vs. 29.3 %), and this was also true concerning dropout because of adverse events (17 % vs. 9.5 %) but not because of lack of efficacy (2.7 % vs. 5.4 %). A quality analysis suggested that although poor quality data might confuse the results, this was not a causal factor for the negative findings of the study. More patients under ziprasidone reported the emergence of adverse events (72.8 % vs. 46.9 %). The presence of mixed features and the specific co-administered mood stabilizer had no effect on the results (Sachs et al. 2011).

Overall the data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers in general suggest that it is not appropriate to add ziprasidone, and levetiracetam should be avoided because there is a risk to worsen depression. Imipramine and venlafaxine might pose the patients at an increased risk of switching to the opposite pole without any visible therapeutic benefits in comparison to other antidepressants.

Add-On Treatment on Lamotrigine

An 8-week study in 29 BD depressed outpatients (62 % BD-I) on a stable dose of lamotrigine (100 mg or more) randomized them to receive either memantine (20 mg/day; $N=14$) or placebo ($N=15$). The results revealed no difference between the two treatment groups at endpoint (Anand et al. 2012).

Add-On Treatment on ECT

A pilot study on 16 BD refractory depressed patients referred for ECT treatment randomized them to thiopental alone ($N=8$) or thiopental plus ketamine (0.5 mg/kg; $N=8$) for anaesthesia before each ECT session. The results of this pilot suggest that ketamine, at a dose of 0.5 mg/kg, given just before ECT, did not enhance the antidepressant effect of ECT (Abdallah et al. 2012).

Other Add-On Options

Another placebo-controlled study on 85 bipolar depressive patients of adjunctive modafinil (177 mg/day) has been shown to improve the outcome of bipolar depression without switching to mania or hypomania. Both the response and remission rates were significantly higher in the modafinil group (44 and 39 %) compared with the placebo group (23 and 18 %) (Frye et al. 2007). Although that study did not report a higher risk for manic switches, it has been reported that modafinil could cause subclinical switches (Fountoulakis et al. 2008b). Also the proof of concept study for the treatment of acute BD-I depression for adjunct armodafinil (the longer-lasting isomer of modafinil; dosage 150 mg/day; $N=128$) on lithium, valproate or olanzapine was positive (Calabrese et al. 2010). The investigation of celecoxib (400 mg/day) did not support its efficacy as an adjunct in the treatment of depressive or mixed episodes (Nery et al. 2008).

Some data support the usefulness of omega-3 fatty acids as adjunctive therapy in bipolar depression but not mania, but the data are conflicting and inconclusive (Sarris et al. 2012; Frangou et al. 2006, 2007; Keck et al. 2006b; Chiu et al. 2005; Stoll et al. 1999; Murphy et al. 2012; Sylvia et al. 2013).

Although there is a wide consensus on the usefulness of ECT both against acute mania and acute bipolar depression and in refractory cases, controlled hard data are lacking (Loo et al. 2010). Another useful tool could be transcranial magnetic stimulation (TMS); however, it has been poorly investigated in bipolar depression (Dell'Osso et al. 2009). Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatment in order to accelerate and sustain the antidepressant response (Wu et al. 2009). One study on bright light therapy in bipolar depression was negative (Dauphinais et al. 2012).

16.2.2.3.3 Conclusions Concerning Combination Treatment and Add-On Treatment

Taken together, the above-mentioned trials suggest that only the OFC has solid scientific support concerning its efficacy against acute bipolar depression. Combination treatment with paroxetine or bupropion with a mood stabilizer does not improve the outcome. In BD depressed patients who experience depression while under lithium

treatment, it is appropriate to add lamotrigine, oxcarbazepine, ketamine or lurasidone but not imipramine. The data on adding paroxetine are equivocal. In BD patients experiencing depression during treatment with valproate, it would be appropriate to add ketamine or lurasidone. In these patients, lurasidone improves also anxiety and ketamine improves suicidality. The data are also negative concerning the adding of memantine on lamotrigine and ketamine simultaneously with ECT.

Overall the data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers in general suggest that it is not appropriate to add ziprasidone. Levetiracetam should be avoided because there is a risk to worsen depression. Imipramine and venlafaxine might pose the patients at an increased risk of switching to the opposite pole without any visible therapeutic benefit in comparison to other antidepressants.

16.2.2.4 Post Hoc Review and Meta-analytic Studies

16.2.2.4.1 Post Hoc Studies

Olanzapine and OFC

A post hoc analysis of the OFC and olanzapine data (Tohen et al. 2003c) reported that in comparison to placebo, the olanzapine-treated patients exhibited statistically significant greater improvements on SF-36 mental component summary (MCS) score and on 3 out of 8 SF-36 dimension scores (mental health, role-emotional and social functioning). The OFC-treated patients exhibited statistically greater improvements on MCS score and on 5 out of 8 SF-36 dimension scores (general health perception, mental health, role-emotional, social functioning and vitality), as well as on QLDS total score vs. both placebo and olanzapine. These results suggest that patients with bipolar depression receiving olanzapine or OFC for 8 weeks had greater improvement in health-related quality of life than those receiving placebo, and additionally OFC treatment is superior to olanzapine alone (Shi et al. 2004a). A second post hoc analysis of the same data set data (Tohen et al. 2003c) reported that the beneficial effect was already present since day 7. A number of alternative methods of analysis of the data (pattern analysis, survival analysis and mixed-effects regression analysis) confirmed the superiority of both olanzapine and OFC vs. placebo (Dube et al. 2007). A sub-analysis of Japanese subpopulation from the second olanzapine study (Tohen et al. 2012) further supported the efficacy of olanzapine in the treatment of bipolar depression (Katagiri et al. 2013). A pooled analysis of the two olanzapine studies (Tohen et al. 2003c, 2012) which utilized LOCF data supported the efficacy of olanzapine on the core depressive items (Tohen et al. 2013).

Quetiapine

There are a number of post hoc analyses which utilize data from two individual quetiapine trials. The first one included both of them (Calabrese et al. 2005a; Thase et al. 2006) and confirmed the efficacy of quetiapine as monotherapy, in comparison to placebo, for the treatment of acute depressive episodes in BD-II disorder (Suppes et al. 2008b). Another post hoc analysis of only one of these trials (Calabrese et al.

2005a) concluded that quetiapine significantly improved quality of life in comparison with placebo, which was evident since week 4. Quetiapine treatment also effected a significant improvement in quality of sleep (Endicott et al. 2007). A further post hoc analysis of the same study (Calabrese et al. 2005a) calculated the number needed to treat (NNT) and reported that the NNT was 5 for both response and remission for quetiapine (600 and 300 mg/day) compared with placebo. It also reported that the median time to response and remission were significantly shorter with quetiapine 600 and 300 mg/day than placebo. There was no difference between the treatment groups in the incidence of treatment-emergent mania or hypomania (quetiapine 600 mg/day: 2.2 %, quetiapine 300 mg/day: 3.9 % and placebo: 3.9 %) (Cookson et al. 2007). Another post hoc analysis of both trials (Calabrese et al. 2005a; Thase et al. 2006) which utilized the data only concerning BD-I patients reported that quetiapine was effective in this subset of patients already since week 1 (MADRS score change at endpoint: quetiapine 300 mg/day = −19.4; 600 mg/day = −19.6; placebo = −12.6; $p<0.001$), and the effect sizes were 0.78 and 0.80, respectively. Changes in MADRS were unrelated to reports of sedation and somnolence (Weisler et al. 2008).

Aripiprazole

One post hoc analysis of pooled data from two similarly designed trials who assessed the impact of aripiprazole monotherapy (Thase et al. 2008) classified patients as severely depressed (Bech-6 total score >15) or less severely depressed (Bech-6 total score <15) and reported that at endpoint the mean reduction in the MADRS total score was not significant in the group of severely depressed patients (aripiprazole: −19.4 vs. placebo: −15.4; $p=0.14$) and neither was in the less severely depressed group (−13.8 vs. −10.3; $p=0.07$). The adverse event profiles were similar between the two severity groups (Thase et al. 2012).

Ziprasidone

The post hoc analysis of the two negative unpublished ziprasidone monotherapy trials confirmed that ziprasidone 40–160 mg/day did not show superiority over placebo at week 6 in the treatment of bipolar depression and detected serious inconsistencies in subject rating that may have limited the ability to detect a difference between drug and placebo response. It also reported that ziprasidone was not efficacious in the more or less severely depressed patients (Lombardo et al. 2012).

Antidepressants

A post hoc analysis of a 6-week trial of imipramine, phenelzine or placebo reported that BD-II depressive patients respond in a similar way unipolars do (Agosti and Stewart 2007).

16.2.2.4.2 Review and Meta-analytic Studies

Lamotrigine which was investigated in five RCTs had a disappointingly negative performance, and all of the studies were negative concerning the primary outcome (Amann et al. 2010). However the fact that there was a kind of positive signal in

some of the secondary outcomes justified the meta-analysis of the data. According to it, the data from 1,072 patients suggested that lamotrigine was superior to placebo in terms of response (on the basis of HAM-D score change: relative risk (RR) = 1.27, 95 % CI: 1.09–1.47, $p=0.002$). The NNT was 11 (95 % CI: 7–25) on HAM-D and 13 (95 % CI: 7–33) on the MADRS. The remission rates were not statistically significantly higher for lamotrigine on HAM-D (pooled RR = 1.10, 95 % CI: 0.90–1.36, $p=0.060$) but were on MADRS (pooled RR = 1.21, 95 % CI: 1.03–1.42, $p=0.021$). There was a significant change in the MADRS total score from baseline ($p=0.04$) but not in the HAM-D ($p=0.08$). There was no difference in the discontinuation rates either ($p=0.292$). Baseline severity of depression seemed to play a significant role, and lamotrigine was superior to placebo in patients with HAM-D score >24 (RR = 1.47, $p=0.001$) but not in those with HAM-D score < or =24 (RR = 1.07, $p=0.445$). In the severe group, the response rate to lamotrigine was 45.5 % vs. 30.1 % in the placebo group, while in the moderate severity group, the response rate to lamotrigine was 47.5 % vs. 44.6 % in the placebo group. According to these data, the interaction by severity was because of a higher response rate in the placebo group in the moderately ill patients, while the response rate to lamotrigine was independent of severity (Geddes et al. 2009).

Three meta-analyses which were published a later reported that only quetiapine and to a lesser extent olanzapine monotherapy exert efficacy in the treatment of bipolar depression. It also reported negative results for lamotrigine and aripiprazole. Both quetiapine and olanzapine analyses suffered from substantial heterogeneity. These authors also comment that although some early lithium RCTs were positive for bipolar depression, they utilized a small study sample and suffered from a number of methodological shortcomings which limit their usefulness (Tamayo et al. 2010; Cruz et al. 2010; De Fruyt et al. 2011). For aripiprazole, the mean Number Needed to Harm (NNTH) for discontinuation due to adverse events during the treatment of acute bipolar depression was 14 and for olanzapine it was 24, while with quetiapine XR treatment the NNTH appeared to be associated with dose, and it was 9 for the 300 mg/day dosage (Gao et al. 2011). A systematic review of the efficacy and safety of SGAs identified seven published papers on the use of aripiprazole, olanzapine and quetiapine. While the internal validity of the trials was fairly good, the external validity was only moderate. Both clinical heterogeneity of the included trials and statistical heterogeneity of the meta-analytic data were considerable. The data were in favour of quetiapine and to a lesser extent of olanzapine, but they were not in favour of aripiprazole. These authors concluded that the adverse events are a major problem of the use of SGAs with weight gain, akathisia and somnolence/sedation being the most frequent and problematic (De Fruyt et al. 2012).

The stringent criteria used by the previous meta-analyses precluded the inclusion of the valproate trials. These four randomized placebo-controlled trials (6- and 8-week duration) were analysed in two meta-analytical studies. The total study sample was small and included only 142 patients, but the quality of the trials was good. The results suggested that divalproex is efficacious vs. placebo both in terms of response rates (39.3 % vs. 17.5 %) as well as remission rates (40.6 % vs. 24.3 %). The relative risks of response (RR = 2.10, $p=0.02$) and remission (RR = 1.61,

$p = 0.04$) were significantly greater for divalproex in comparison to placebo (Bond et al. 2010). The standardized effect size concerning the change from baseline in the depressive scales was statistically significant (–0.35), but the effect on anxiety symptoms was not. There was no evidence of induction of manic symptoms, and there was no difference in the adverse events rate (Smith et al. 2010). Similarly, the meta-analysis of the two negative aripiprazole studies produced positive results with a standardized effect size equal to 0.17 (Fountoulakis et al. 2011b).

Another meta-analysis focused on depressed patients with BD-II. The authors included studies with different methodology (monotherapy and add-on, with or without placebo, double-blind as well as open and acute together with maintenance studies) and reported that according to their results, quetiapine was judged as having compelling evidence supporting its efficacy, while there was some support for the efficacy of lithium, antidepressants and pramipexole. The data for lamotrigine were equivocal (Swartz and Thase 2011).

The first meta-analysis concerning antidepressants included 12 studies with variable designs and suggested that antidepressants are both effective and safe for bipolar depression (Gijsman et al. 2004). However subsequent analyses on 15 antidepressant trials suggested that antidepressants as a class are no more efficacious than placebo, and they do not increase the risk of switching to the opposite pole (Sidor and Macqueen 2010, 2012). The opposite conclusion has been reported by another more recent analysis which reported that overall there is a positive signal for antidepressants and that the risk for switching to mania is overestimated (Vazquez et al. 2013).

Another meta-analysis on 18 RCTs compared the efficacy, acceptability and safety of mood stabilizer monotherapy with combination and antidepressant treatment. The results suggested that mood stabilizer monotherapy was associated with increased rates of response (RR = 1.30, NNT = 10) and remission (RR = 1.51, NNT = 8) in comparison to placebo. Combination therapy was not statistically superior to monotherapy, and there were no differences between individual medications or drug classes (Van Lieshout and MacQueen 2010). However it is clear that a class effect is not present concerning antidepressants in bipolar depression (Fountoulakis et al. 2011a). Moreover, the utilization of the 'class effect' concept in meta-analytic studies produces erroneous results like 'Mood stabilisers are moderately efficacious' (Van Lieshout and MacQueen 2010).

A recent meta-analysis of data concerning BD-I and BD-II depression suggested that patients who do not respond in the first 2 weeks of treatment are unlikely to respond eventually and would benefit from a change in treatment. It analysed the data from 1,913 patients which had been randomized to aripiprazole, lamotrigine, olanzapine, OFC or quetiapine and from 1,456 which had received placebo. Early improvement predicted response and remission with high sensitivity (86 and 88 %, respectively), but rates of false positives were high (53 and 59 %, respectively). The pooled negative predictive values for response/remission were 74 and 82 %, respectively, with low rates of false negatives (14 and 12 %, respectively). These results suggest that although early improvement does not predict eventual response or remission its absence predicts of eventual nonresponse. Thus clinicians can have an idea when to change treatment because of lack of efficacy during short-term treatment, and 2 weeks seem to be a reasonable time point to consider a change in therapy (Kemp et al. 2010).

Another recent meta-analysis on the efficacy of quetiapine, lamotrigine, paroxetine, lithium, olanzapine, aripiprazole, phenelzine and divalproex included 19 trials and reported that not all medications were associated with symptomatic improvement, with lamotrigine, paroxetine, aripiprazole and lithium not being different from placebo. The highest reductions in MADRS scores vs. placebo were reported for the OFC (–6.6; $p=0.000$) and quetiapine monotherapy (for 300 mg/day, –4.8; $p=0.000$; for 600 mg/day, –4.8; $p=0.000$), with quetiapine monotherapy also showing the highest reduction in HAM-D scores (–4.0; $p=0.000$) (Vieta et al. 2010a). A meta-analysis confirmed the superiority of OFC vs. olanzapine monotherapy (RR = 1.58; 95 % CI: 1.27–1.97) and vs. placebo (RR = 1.99; 95 % CI: 1.49–2.65) but not to lamotrigine; however, the authors noted that these data were of low quality. Similar results were found for remission and relapse rates. No differences were identified for levels of depression and mania symptoms (low-quality evidence) and incidence of mania (moderate-quality evidence). Adverse effects were more common in patients treated with OFC than in those treated with lamotrigine, but no difference was found relative to the patients treated with olanzapine monotherapy (Silva et al. 2013). A systematic review from all antiepileptics supported the use only of divalproex and lamotrigine in the treatment of acute bipolar depression (Reinares et al. 2013).

A meta-analysis which pooled data from nine randomized, double-blind, placebo-controlled, acute studies of ziprasidone including the two unpublished in bipolar depression reported that the discontinuation rate due to adverse events or 7 % or greater weight gain between ziprasidone and placebo was not significant in all psychiatric conditions. In bipolar depression the risk for akathisia with ziprasidone had an NNTH = 44, and reported somnolence had NNTH = 8 which seemed to be dose dependent (Gao et al. 2013).

Two reviews investigated the issue of the treatment of refractory bipolar depression and identified several open but only seven RCTs, of whom two with (ar) modafinil and ECT and one with each ketamine, lamotrigine, pramipexole, inositol and risperidone. Therefore these authors concluded that the available hard data for treatment strategies in resistant bipolar depression is extremely scarce, and most of the strategies remain essentially experimental; however, they seem to be efficacious and promising (Sienaert et al. 2013; Aan Het Rot et al. 2012).

One meta-analysis compared the efficacy of ECT in unipolar vs. bipolar depression and identified six relevant studies. It reported a similar rate of response (50.9 % vs. 53.2 %) (Dierckx et al. 2012).

16.2.3 Maintenance Treatment

16.2.3.1 Monotherapy

A summary of monotherapy data for maintenance treatment is shown in Table 16.6.

16.2.3.1.1 Lithium

There is a number of old small studies which investigated the usefulness of lithium in the maintenance treatment of BD, and all of them reported positive findings concerning the efficacy of lithium. However these studies are problematic not only

because the study samples were often mixed and as small as with only 15 (Melia 1970), 18 (Fyro and Petterson 1977), 53 (Fieve et al. 1976) and 24 patients (Cundall et al. 1972) but also because they followed a methodological approach which is no longer considered adequate in psychopharmacology research. Thus, although there are several studies with mixed and small samples and inadequate design (Hullin et al. 1972; Klein et al. 1981; Prien et al. 1973b; Fieve et al. 1976), small non-randomized case-control studies with placebo (Margo and McMahon 1982; Persson 1972), small crossover studies (Mander and Loudon 1988) and discontinuation studies (Post et al. 1992; Baastrup et al. 1970; Small et al. 1971; Christodoulou and Lykouras 1982; Melia 1970; Cundall et al. 1972; Hullin et al. 1972), conclusions are impossible since these trials are difficult to interpret.

Most of these early studies suggested that lithium is efficacious for the prophylaxis against both manic and depressive episodes in both BD-I and BD-II patients (Dunner et al. 1976; Prien et al. 1973a, b; Kane et al. 1982). However in one of them, the efficacy of lithium in the prevention of bipolar depression has been questioned. That study was in 205 BD patients who were hospitalized because of acute mania. It reported that lithium was superior to placebo in preventing relapses, and this was due mainly to the lower incidence of manic relapses in the lithium group (Prien et al. 1973a). Interestingly, in another study a discontinuation-induced refractoriness phenomenon was described for the first time (Post et al. 1992).

The first properly conducted randomized, double-blind, parallel-group multicentre study concerning lithium took part in 2000 and included 372 BD patients who met the inclusion criteria within 3 months of the onset of an index manic episode. These patients were randomized to maintenance treatment with lithium (0.8–1.2 mmol/l; $N=91$), divalproex (75–125 μg/ml; $N=372$) or placebo ($N=94$) for a period of 52 weeks. The patients should have been randomized within 3 months from the onset of the index episode, and they were required to be manic, partially recovered or remitted but not depressed at randomization. They were required to fulfil the inclusion criteria for two subsequent assessments, 6 days apart from each other. The three treatment groups did not differ concerning the time to manifestation of any mood episode, and this was also the case concerning manic or depressive episodes alone. The median times to 50 % survival without a mood episode were 24, 40 and 28 weeks, respectively. The lithium group had higher rates of tremor, thirst and polyuria (Bowden et al. 2000).

Another study utilized an 8–16-week open-label lamotrigine treatment of 349 BD-I patients (rapid cycling excluded, polarity was balanced) with acute mania/hypomania. Other psychotropic drug regimens were discontinued, and 175 patients who responded and maintained a CGI score of 3 or less for 4 consecutive weeks were randomized to lithium (0.8–1.1 mEq/l; $N=46$) or lamotrigine (100–400 mg/day; $N=59$) or placebo ($N=70$) as double-blind maintenance treatment for 18 months. The results suggested that both lithium ($p=0.006$) and lamotrigine ($p=0.02$) were superior to placebo at prolonging the time to intervention for any mood episode. The median survival times were 292, 140 and 85 days, respectively. Lamotrigine was superior to placebo at prolonging the time to a depressive episode, while lithium was superior to placebo at prolonging the time to a manic, hypomanic

or mixed episode. The most common adverse event reported for lithium was diarrhoea. The interpretation of this study is complex, because the study sample was enriched for response to lamotrigine, although lamotrigine is not efficacious against acute manic or mixed episodes. Thus, one interpretation could be that the study sample comprised of patients which manifested spontaneous remission (Bowden et al. 2003). A study with a similar design but on 966 BD-I depressed patients (rapid cycling excluded) utilized open-label lamotrigine (titrated to 200 mg/day) for 8–16 weeks during which period concomitant drugs were gradually withdrawn. Those patients who responded and maintained a CGI score of 3 or less for 4 consecutive weeks ($N=463$) were then randomly assigned to lithium (0.8–1.1 mEq/l; $N=121$), lamotrigine (50, 200, or 400 mg/day; $N=221$) or placebo ($N=121$) monotherapy for up to 18 months. The results suggested that the time to intervention for any mood episode was statistically superior ($p=0.029$) for both lithium and lamotrigine vs. placebo. The median survival times were 170, 200 and 93 days, respectively. Lamotrigine was significantly superior to placebo at prolonging the time to intervention for a depressive episode ($p=0.047$) while lithium at prolonging the time to intervention for a manic or hypomanic episode ($p=0.026$). There was no difference in the proportion of patients who were intervention-free for depression (46 % vs. 57 % vs. 45 %) or mania (86 % vs. 77 % vs. 72 %) at 1 year. Headache was the most frequent adverse event for all three treatment groups (Calabrese et al. 2003a).

Also there is one short-term placebo-controlled discontinuation study which assessed the efficacy and safety of lithium for the maintenance treatment of BD in adolescents. Participants with acute mania ($N=100$) received open treatment with lithium at therapeutic serum levels (mean 0.99 mEq/l) for at least 4 weeks. The patients who responded ($N=40$) were randomly assigned to continue ($N=19$) or discontinue lithium ($N=21$) during a 2-week double-blind, placebo-controlled phase. There was no significant difference between the two groups in terms of experiencing a clinically significant symptom exacerbation during the 2-week double-blind phase (52.6 % under lithium vs. 61.9 % under placebo) (Kafantaris et al. 2004).

Finally there is also one recent study (NCT00314184 or trial 144, also named 'SPARCLE') which investigated the efficacy and safety of lithium vs. quetiapine (300–800 mg/day) vs. placebo as maintenance treatment in BD-I. During the open-label phase, 2,438 BD-I patients with a current or recent manic, depressive or mixed episode received open-label quetiapine, and those achieving stabilization ($N=1,226$; 50.3 %) were randomized to continue quetiapine or to switch to placebo or lithium (0.6–1.2 mEq/l) for up to 104 weeks in a double-blind trial. The study was terminated early after planned interim analysis provided positive results. The results suggested that the time to recurrence of any mood event was significantly longer for lithium and for quetiapine vs. placebo ($p<0.0001$). Both lithium and quetiapine significantly increased time to recurrence of both manic events and depressive events compared with placebo. Overall rates of adverse events were generally similar between treatment groups (Weisler et al. 2011).

Overall there are four large randomized placebo-controlled studies (plus one small) concerning the efficacy of lithium in the maintenance treatment of BD. One

is negative and three are positive. Two positive studies support the usefulness of lithium in the prevention of manic but not depressive episodes irrespective of the polarity of the index episodes. The third study supports its usefulness in the prevention of depressive episodes also. There are some data concerning index mixed episodes, but there are no data supporting the efficacy in the prevention of mixed episodes. There are no specific data concerning rapid cycling patients. The study samples were not enriched for response to lithium and probably contained a significant proportion of patients in spontaneous improvement since lamotrigine is neither active in acute mania nor in acute depression. One study had a sample enriched for response to quetiapine. The design of the studies was somewhat problematic, especially concerning the magnitude of improvement during the acute treatment phase and the duration the patients were stable before entering the double-blind phase.

16.2.3.1.2 Valproate

As mentioned above, there is one properly conducted randomized, double-blind, parallel-group multicentre study concerning valproate. That study included 372 BD patients who met the recovery criteria within 3 months of the onset of an index manic episode. These patients were randomized to maintenance treatment with divalproex (75–125 μg/ml; $N=372$) or lithium (0.8–1.2 mmol/l; $N=91$) or placebo ($N=94$) for a period of 52 weeks. The patients should have been randomized within 3 months from the onset of the index episode, and they were required to be manic, partially recovered or remitted but not depressed at randomization. They were required to fulfil the inclusion criteria for two subsequent assessments, 6 days apart from each other. The three treatment groups did not differ concerning the time to manifestation of any mood episode, and this was also the case concerning manic or depressive episodes alone. The divalproex group had higher rates of tremor, sedation, weight gain and reduction in platelet blood count (Bowden et al. 2000).

This study is the only one available so far concerning the efficacy of valproate. Valproate was the agent under investigation, while lithium served as active control. Taking into consideration the fact that lithium has proven efficacy in the prevention of mood episodes, this should be considered to be a failed study and not negative for valproate.

16.2.3.1.3 Carbamazepine

Similarly, the data are essentially absent for carbamazepine. There is only a small old study with an inadequate design, which applied carbamazepine 200–600 mg/day for 1 year in 32 patients (22 on agent and 10 on placebo). The results suggested that more patients under carbamazepine had a good response in comparison to placebo (60 % vs. 22.2 %), but the difference was not significant because of the small study sample (Okuma et al. 1981).

16.2.3.1.4 Lamotrigine

There are three trials which investigate the efficacy and safety of lamotrigine in the maintenance treatment of BD. In the first study, open-label lamotrigine was added to current treatment of 324 BD patients with rapid cycling bipolar disorder. From those

patients, 182 were stabilized. Psychotropics were tapered off, and these patients were randomly assigned to lamotrigine or placebo monotherapy for 6 months. The results suggested that the two treatment groups were similar in terms of time to additional pharmacotherapy, which was the primary outcome. However, survival in the study was statistically different between the treatment groups ($p=0.036$) and also was the median survival time ($p=0.03$), both in favour of the lamotrigine group. More patients under lamotrigine were stable without relapse for 6 months of monotherapy (41 % vs. 26 %; $p=0.03$). There were no treatment-related changes in laboratory parameters, vital signs or body weight, and no serious rashes occurred (Calabrese et al. 2000).

The next two studies both utilized a similar design. The first of them utilized an 8–16-week open-label lamotrigine treatment of 349 patients (rapid cycling excluded) with acute mania/hypomania. Other psychotropic drug regimens were discontinued, and the 175 patients who responded and maintained a CGI score of 3 or less for 4 consecutive weeks were randomized to lamotrigine (100–400 mg/day; $N=59$) or lithium (0.8–1.1 mEq/l; $N=46$) or placebo ($N=70$) as double-blind maintenance treatment for 18 months. The results suggested that both lamotrigine ($p=0.02$) and lithium ($p=0.006$) were superior to placebo at prolonging the time to intervention for any mood episode. Lamotrigine was superior to placebo at prolonging the time to a depressive episode, while lithium was superior to placebo at prolonging the time to a manic, hypomanic or mixed episode. The most common adverse event reported for lamotrigine was headache and diarrhoea for lithium (Bowden et al. 2003). A study with a similar design but on 966 BD-I depressed patients (rapid cycling excluded) utilized open-label lamotrigine (titrated to 200 mg/day) for 8–16 weeks during which period concomitant drugs were gradually withdrawn. Those patients who responded and maintained a CGI score of 3 or less for 4 consecutive weeks ($N=463$) were then randomly assigned to monotherapy with lamotrigine (50, 200 or 400 mg/day; $N=221$), lithium (0.8–1.1 mEq/l; $N=121$) or placebo ($N=121$) for up to 18 months. The results suggested that the time to intervention for any mood episode was statistically superior ($p=0.029$) for both lamotrigine and lithium vs. placebo. The median survival times were 200, 170 and 93 days, respectively. Lamotrigine was statistically superior to placebo at prolonging the time to intervention for a depressive episode ($p=0.047$) while lithium at prolonging the time to intervention for a manic or hypomanic episode ($p=0.026$). There was no difference in the proportion of patients who were intervention-free for depression (46 % vs. 57 % vs. 45 %) or mania (86 % vs. 77 % vs. 72 %) at 1 year. Headache was the most frequent adverse event for all 3 treatment groups (Calabrese et al. 2003a).

Overall there are three randomized placebo-controlled studies concerning the efficacy of lamotrigine in the maintenance treatment of BD and specifically in the prevention of depressive but not of manic episodes. This efficacy was present irrespective of the polarity of the index episodes. There are no data concerning index mixed episodes or features. Although the only study on rapid cycling patients was negative concerning the primary outcome, it provided some positive data concerning the secondary outcomes. Although technically the study samples were enriched for response to lamotrigine, probably they contained a significant proportion of patients in spontaneous improvement since lamotrigine is not efficacious neither in

acute mania nor in acute bipolar depression. The design of the studies was somewhat problematic, especially concerning the magnitude of improvement during the acute treatment phase and the duration the patients were stable before entering the double-blind phase.

16.2.3.1.5 Antidepressants

In the first published study, 44 BD patients with an index episode of depression, after remission, were randomly assigned to lithium carbonate, imipramine or placebo for 2 years. The results suggested that imipramine was similar to placebo and inferior to lithium. The difference between treatments was due primarily to depressive episodes; manic episodes occurred infrequently (Prien et al. 1973b). Another early small study on 22 BD-II patients in remission for at least 6 months, which were treated openly with imipramine 150 mg/day, randomly assigned them on a double-blind basis to treatment with lithium, imipramine, lithium carbonate plus imipramine or placebo. Lithium was found to prevent any type of relapse among patients BD-II; however, imipramine was no better than placebo (Kane et al. 1982).

A placebo-controlled study in 839 depressed patients, which investigated the efficacy and safety of short- and long-term fluoxetine treatment, compared in a retrospective way the results concerning patients with BD-II ($n=89$) with those concerning patients with unipolar depression (UP; $N=661$ unmatched and 89 matched). All patients received 12 weeks of open-label 20 mg/day fluoxetine therapy. Complete remission was defined as a total HAM-D score ≤ 7 by week 9 that was then maintained for 3 additional weeks. Remitted patients were then randomly assigned to receive double-blind treatment with one of the following: (1) fluoxetine 20 mg daily for 52 weeks; (2) fluoxetine for 38 weeks, then placebo for 14 weeks; (3) fluoxetine for 14 weeks, then placebo for 38 weeks; or (4) placebo for 52 weeks. The results suggested that fluoxetine had similar efficacy in the two groups during the long-term relapse prevention therapy. More BD-II patients experienced a manic switch, but this was not statistically significant (Amsterdam et al. 1998).

In another trial, 37 BD-II and BD-NOS patients in a depressive episode received open-label fluoxetine monotherapy 20 mg/day for up to 8 weeks. The 12 patients who responded (HAM-D ≤ 9) were randomized to receive continuation therapy with fluoxetine 20 mg/day or placebo for up to 6 months. During the continuation phase, 43 % of fluoxetine-treated patients and 100 % of placebo-treated patients relapsed ($p=0.08$). Fluoxetine-treated patients had a small but significant increase in YMRS score in comparison to placebo (3.0 vs. 0.2; $p=0.01$), but no hypomanic switch episodes were observed. Overall the study sample was too small to permit valid conclusions (Amsterdam and Shults 2005b). Finally, one trial examined the safety and efficacy of long-term (50 weeks) fluoxetine monotherapy (10–40 mg/day; $N=28$) vs. lithium monotherapy (300–1,200 mg/day; $N=26$) and vs. placebo ($N=27$) in the preventing of relapse and recurrence of depressive episodes in BD-II patients. There was a significantly prolonged mean time to relapse in the fluoxetine group in comparison to the others (249.9 days vs. 156.4 days vs. 186.9; $p=0.03$). There were no statistically significant differences in hypomanic symptoms among treatment groups over time (Amsterdam and Shults 2010).

Overall two small old studies were negative concerning the value of imipramine in the prevention of depressive episodes in BD. Three other small studies provide some support for the usefulness of fluoxetine monotherapy in the prevention of depressive episodes in BD-II patients. All studies suffer from methodological problems and are essentially continuation studies.

16.2.3.1.6 Olanzapine

The first trial included 361 BD-I patients with an index manic or mixed episode in at least partial remission for 2 consecutive weekly visits after olanzapine 5–20 mg/day open-label treatment of the acute phase. These patients were randomized to receive olanzapine ($N=225$) or placebo ($N=136$) for up to 48 weeks. The results suggested that the median time to symptomatic relapse into any mood episode was significantly longer among patients receiving olanzapine vs. placebo (174 days vs. 22). The times to symptomatic relapse into manic, depressive and mixed episodes were all significantly longer among patients receiving olanzapine than among patients receiving placebo. The relapse rate to any mood episode was significantly lower in the olanzapine group (46.7 % vs. 80.1 %), and this was also true concerning any type of episode. During olanzapine treatment, the most common emergent event was weight gain. Placebo patients lost a mean of 2.0 kg while in contrast patients in the olanzapine group gained 1.0 kg (Tohen et al. 2006).

A second study on 766 BD-I patients with current manic or mixed episodes (rapid cycling excluded) which were initially randomized to flexibly dosed paliperidone ER (3–12 mg/day; $N=617$) or olanzapine (5–20 mg/day; $N=149$) for a duration of 3-week acute treatment phase. The responders continued the same treatment (12-week continuation phase). Those patients on paliperidone ER who achieved remission during this phase were randomized to fixed-dose paliperidone ER ($N=152$) or placebo ($N=148$), while those on olanzapine continued to receive that at a fixed dose ($N=83$). This maintenance phase continued until at least 140 recurrences occurred among patients originally assigned to paliperidone ER in the acute treatment phase. The median time to recurrence of any mood symptoms was significantly longer for paliperidone vs. placebo (558 vs. 283 days; $p=0.017$) and not observed with olanzapine (<50 % of patients experienced recurrence). Olanzapine-treated patients had significantly longer time to recurrence for any mood symptoms in comparison to either group ($p<0.001$). For paliperidone the difference was significant for preventing recurrence of manic, but not depressive symptoms. This clarification is not reported concerning olanzapine. Treatment-emergent adverse events occurred more often in olanzapine group (64 %) than placebo (59 %) or paliperidone ER groups (55 %) (Berwaerts et al. 2012a).

Finally, one trial utilized a 12-week open-label period with risperidone long-acting injection (RLAI) in 560 patients with manic or mixed episode (rapid cycling excluded). Those who did not experience a recurrence entered an 18-month randomized, double-blind period with oral olanzapine (10 mg/day; $N=131$), RLAI ($N=132$) or placebo ($N=135$). Time to recurrence of any mood episode was significantly longer with olanzapine and RLAI vs. placebo ($p = p<0.001$ and 0.031). Again the difference concerning the time to recurrence was significant for both mania and

depression concerning olanzapine ($p<0.001$ and $p=0.01$) and for mania ($p=0.005$) but not depression ($p=0.655$) concerning RLAI. Fewer patients in the olanzapine and RLAI groups relapsed into any mood episode in comparison to placebo (23.8 % vs. 38.9 % vs. 56.4 %). Both medication arms manifested lower relapses into mania (14.6 % vs. 19.8 % vs. 39.1 %), but only olanzapine manifested fewer relapses also concerning depression (9.2 % vs. 19.1 % vs. 17.3 %) (Vieta et al. 2012).

These results provide support for the efficacy of olanzapine in the prevention of any kind of mood relapse after an index manic or mixed episode which responded to olanzapine treatment during the acute phase. However the efficacy of olanzapine does not seem to be restricted to those patients who responded to olanzapine during the acute phase. Its effect on rapid cycling patients is unknown.

16.2.3.1.7 Aripiprazole

There are two trials supporting the efficacy of aripiprazole during the maintenance phase of BD. In the first one, which took place in 76 centres in 3 countries, 161 recently manic- or mixed-episode BD-I patients stabilized on aripiprazole (15 or 30 mg/day, 6–18 weeks) and maintained on aripiprazole treatment for 6 weeks were randomized to aripiprazole ($N=78$) or placebo ($N=83$) for 26 weeks. The results suggested that aripiprazole was superior to placebo in delaying the time to relapse ($p=0.020$), and this was specifically due to a significant delay in the development of manic ($p=0.01$) but not depressive ($p=0.68$) relapses. Aripiprazole-treated patients had significantly fewer relapses than placebo patients (25 % vs. 43 %; $p=0.013$). The adverse events related with aripiprazole treatment were weight gain (13 % vs. 0 %) and akathisia, pain in the extremities, tremor and vaginitis (Keck et al. 2006a). A second study included a 26-week, double-blind, placebo-controlled relapse prevention with a prospective, 74-week, double-blind, placebo-controlled extension phase (100 weeks in total) in 567 BD-I patients with a recent manic or mixed episode who had received open-label aripiprazole 15 or 30 mg/day (started at 30 mg/day) for 6–18 weeks. Those patients who achieved stabilization ($N=161$; YMRS ≤ 10 and MADRS ≤ 13 for 6 consecutive weeks) were randomly assigned to double-blind treatment with aripiprazole ($N=78$) or placebo ($N=83$) for 26 weeks. Patients who completed the 26-week stabilization continued in a double-blind fashion with aripiprazole ($N=39$) or placebo ($N=27$) for an additional 74 weeks and were monitored for relapse, efficacy and tolerability. At 100 weeks, time to relapse was significantly longer with aripiprazole than placebo ($p=0.01$). The rate of relapse was 33 % in the aripiprazole group vs. 52 % in the placebo group at endpoint. Aripiprazole was superior to placebo in delaying time to manic relapse ($p=0.005$) but not to depressive relapse ($p=0.602$). Eventually only seven patients in the aripiprazole group and five in the placebo group completed the 100 weeks of the study, and this should be considered vs. the 567 who entered the 6–18 weeks of the stabilization phase. The adverse events reported during 100 weeks of treatment with aripiprazole vs. placebo were tremor, akathisia, dry mouth, hypertension, weight gain, vaginitis, abnormal thinking, pharyngitis and flu syndrome. Mean weight change from baseline to 100 weeks (LOCF) was +0.4 kg with aripiprazole and −1.9 kg with placebo (Keck et al. 2007).

Overall these two trials support the efficacy of aripiprazole in the maintenance treatment of BD but only concerning the prevention of manic but not depressive episodes in patients after an index manic or mixed episode who responded to aripiprazole during the acute phase. These two correspond to stringent criteria concerning the definition of 'maintenance' treatment.

16.2.3.1.8 Quetiapine

There is one published positive study that used quetiapine IR (NCT00314184 or trial 144, also named 'SPARCLE') which investigated the efficacy and safety of quetiapine monotherapy (300–800 mg/day) as maintenance treatment in BD-I patients compared with switching to placebo or lithium. During the open-label phase, 2,438 BD-I patients with a current or recent manic, depressive or mixed episode received open-label quetiapine, and those achieving stabilization ($N=1,226$; 50.3 %) were randomized to continue quetiapine or to switch to placebo or lithium (0.6–1.2 mEq/l) for up to 104 weeks in a double-blind fashion. The study was terminated early after planned interim analysis provided positive results. The results suggested that the time to recurrence of any mood event was significantly longer for quetiapine vs. placebo ($p<0.0001$) and for lithium vs. placebo ($p<0.0001$). Both quetiapine and lithium significantly increased time to recurrence of both manic events and depressive events compared with placebo. Overall rates of adverse events were generally similar between treatment groups, and safety findings for quetiapine were consistent with its known profile (Weisler et al. 2011).

16.2.3.1.9 Paliperidone

There is one study on 766 BD-I patients with current manic or mixed episodes (rapid cycling excluded) which were initially randomized to flexibly dosed paliperidone ER (3–12 mg/day; $N=617$) or olanzapine (5–20 mg/day; $N=149$) for a duration of 3-week acute treatment phase. The responders continued the same treatment (12-week continuation phase). Those patients on paliperidone ER who achieved remission during this phase were randomized to fixed-dose paliperidone ER ($N=152$) or placebo ($N=148$), while those on olanzapine continued to receive that at fixed dose ($N=83$). This maintenance phase continued until at least 140 recurrences occurred among patients originally assigned to paliperidone ER in the acute treatment phase. The median time to recurrence of any mood symptoms was significantly longer for paliperidone vs. placebo (558 vs. 283 days; $p=0.017$) and not observed with olanzapine (<50 % of patients experienced recurrence). Olanzapine-treated patients had significantly longer time to recurrence for any mood symptoms in comparison to either group ($p<0.001$). For paliperidone the difference was significant for preventing recurrence of manic, but not depressive symptoms. Treatment-emergent adverse events occurred more often in olanzapine group (64 %) than placebo (59 %) or paliperidone ER groups (55 %) (Berwaerts et al. 2012a). Overall this trial supports the usefulness of paliperidone maintenance treatment for the prevention of manic recurrences in patients with index manic or mixed episodes who responded to paliperidone during the acute phase.

16.2.3.1.10 Risperidone Long-Acting Injectable (RLAI)

The first study on the efficacy of RLAI in the maintenance treatment of BD-I was conducted in 559 BD-I patients with current or recent manic or mixed episode (rapid cycling excluded). The patients were treated with open-label oral risperidone for 3 weeks and open-label RLAI for 26 weeks. Those patients who maintained response ($N=303$) were randomly allocated to continue RLAI ($N=154$) or to placebo injections ($N=149$) for up to 24 months. Most patients (77 %) on RLAI received a dose of 25 mg every 2 weeks. The results suggested that the time to recurrence for any mood episode was significantly longer in the RLAI group vs. placebo ($p<0.001$); the difference was significant for time to recurrence of mania ($p<0.001$) but not time to recurrence of depression ($p=0.805$). Fewer patients in the RLAI group experienced recurrence in comparison to placebo (30 % vs. 56 %). Weight gain was more in the risperidone group (Quiroz et al. 2010). The second trial utilized a 12-week open-label period with RLAI in 560 patients with manic or mixed episode (rapid cycling excluded). Those who did not experience a recurrence entered an 18-month randomized, double-blind period with RLAI ($N=132$) or placebo ($N=135$) or oral olanzapine (10 mg/day; $N=131$). Of patients under RLAI, 25 mg were received by 66 % of patients, 37.5 mg by 31 % and 50 mg by 4 %. The results demonstrated a median time to mood episode recurrence of 198 days in the placebo arm, whereas the median was not reached in the RLAI arm ($p=0.057$). Time to recurrence of any mood episode was significantly longer with RLAI and olanzapine vs. placebo ($p=0.031$ and $p<0.001$). Again the difference was significant for time to recurrence of mania ($p=0.005$) but not depression ($p=0.655$) concerning RLAI but for both concerning olanzapine ($p<0.001$ and $p=0.01$). Fewer patients in the RLAI and olanzapine groups relapsed into any mood episode in comparison to placebo (38.9 % vs. 23.8 % vs. 56.4 %). Both medication arms manifested lower relapses into mania (19.8 % vs. 14.6 % vs. 39.1 %), but only olanzapine manifested fewer relapses also concerning depression (19.1 % vs. 9.2 % vs. 17.3 %). There was no evidence of worsening of depression in the RLAI arm (Vieta et al. 2012).

Overall the data suggest that RLAI is efficacious in the prevention of manic but not depressive episodes in BD-I patients with a manic or mixed index episode who responded to oral risperidone or RLAI during the acute phase. No data concerning the efficacy in rapid cycling patients exist.

16.2.3.1.11 Conclusions of Monotherapy Trials

The data that come from placebo-controlled monotherapy trials suggest that lithium, aripiprazole, paliperidone and RLAI are efficacious in the prevention of manic episodes in patients who recovered from an index manic or mixed episode. Olanzapine and quetiapine were efficacious in the prevention of both manic and depressive episodes. Quetiapine was efficacious irrespective of index episode, while olanzapine was proven efficacious in the prevention of mixed episodes also. There are no data for carbamazepine or valproate (failed study).

Irrespective of index episode, lamotrigine is efficacious in the prevention of depressive but not manic episodes and was not efficacious in the prevention of mixed episodes or in rapid cycling patients. The data were negative for imipramine, while there was some support for the efficacy of fluoxetine in BD-II patients.

All except lithium and maybe olanzapine were proven efficacious in samples enriched for response during the acute phase. Except from the negative data concerning lamotrigine, there are no data concerning rapid cycling patients. Also except from the data concerning olanzapine, there are no data concerning specifically the prevention of mixed episodes or the response of patients at an index mixed episode.

16.2.3.2 Comparison of Treatments

16.2.3.2.1 Lithium Versus Others

Lithium Versus Carbamazepine

There are a number of studies comparing lithium with carbamazepine. The first study included 83 in- and outpatients suffering from major affective, schizoaffective or schizophreniform psychoses. The duration was 3 years, and it was a prospective double-blind randomized trial. There was no difference between lithium and carbamazepine with two-thirds of patients responding well to either agent. There was a significantly higher dropout rate for patients with mood-incongruent psychotic features in the lithium group. Both drugs appeared more effective in preventing excited rather than depressive symptoms (Placidi et al. 1986). Another trial reported some superiority for lithium (Watkins et al. 1987), while two others reported that the two agents had comparative efficacy (Lusznat et al. 1988; Stoll et al. 1989).

A study on 52 hospitalized acutely manic patients randomized them to treatment with either lithium or carbamazepine after a 2-week drug withdrawal period for up to 2 years. Double-blind assessments revealed no significant differences between the two treatment groups (Small et al. 1991). Another 12-month double-blind trial in 31 BD patients who were previously stabilized on lithium randomized them to receive either lithium ($N=16$) or carbamazepine ($N=15$) and reported that the overall relapse rate was similar in the two treatment groups (Coxhead et al. 1992). A 2-year duration open trial suggested that there was no significant difference between the two medication arms (Simhandl et al. 1993). An interesting study randomized 52 outpatients with BD to receive lithium or carbamazepine, a crossover to the opposite drug in the second year and then a third year on the combination. There was no difference between the treatment groups in terms of marked or moderate improvement (33.3 % vs. 31.4 % vs. 55.2 %). Lithium was superior to carbamazepine in the prophylaxis of mania. Patients with a past history of rapid cycling did poorly on monotherapy and better on combination treatment (28.0 % vs. 19.0 % vs. 56.3 %; $p<0.05$) (Denicoff et al. 1997).

One of the most important is the MAP study which took place in nine university hospitals in Germany. It included 144 BD patients which were randomized to open treatment with lithium ($N=74$; mean serum level 0.63 mmol/l) vs. carbamazepine ($N=70$; mean dosage 621 mg/day) for 2.5 years. There was no difference between the two drugs in terms of number of recurrences. There was some superiority of lithium when comedication ($p=0.041$) or adverse effects ($p=0.007$) was taken into consideration. More patients in the carbamazepine group dropped out (5.4 % vs. 12.9 %) although more patients in the lithium group reported any adverse event

(61 % vs. 21 %; $p<0.001$). In those patients who completed the 2.5 years of the study, there was a higher but not significant number of recurrences in the carbamazepine group (47 % vs. 28 %; $p=0.06$). Overall there was no difference between the two agents although there was a trend for lithium to perform better concerning some secondary outcomes (Greil et al. 1997). A further analysis of the study sample separated BD-I ($N=114$) vs. BD-II and BD NOS ($N=57$). Lithium was superior in BD-I patients, while there was no difference between the two agents in the second subsample. A second sub-analysis contrasted a 'classical subgroup' (BD-I without mood-incongruent delusions and without comorbidity; $N=67$) and a 'nonclassical subgroup' (all other patients $N=104$). Lithium was superior in the 'classical' group with a significantly lower hospitalization rate (26 vs. 62 %; $p=0.012$), while there was no difference between the two agents in the 'nonclassical' group, although a tendency in favour of carbamazepine was found. The results did not find any effect concerning the episode sequence prior to the index episode although there was a tendency of the pattern mania–depression-free interval to respond better to lithium. There was also a trend for suicidal behaviour to respond better to lithium, but the data on patients' satisfaction were significantly in favour of carbamazepine. Overall the results of this sub-analysis suggest that lithium has a global efficacy in BD, while the effect of carbamazepine might be restricted to the 'nonclassical' patients (Kleindienst and Greil 2000; Greil and Kleindienst 1999a, b). A further analysis of the data suggested that after taking a variety of outcomes into consideration (interepisodic morbidity, dropout and rehospitalization), lithium had superior performance in comparison to carbamazepine (Kleindienst and Greil 2002).

A 2-year duration double-blind study in 94 BD patients with at least two mood episodes during the previous 3 years who were in remission at entry into the study compared lithium ($N=44$) vs. carbamazepine ($N=50$). These patients were not treated with lithium or carbamazepine for more than a total of 6 months during their lifetime. No concurrent antipsychotics or antidepressants were allowed. Fewer patients under lithium relapsed into any mood episode (27.3 % vs. 42 %). Lithium was superior to carbamazepine in those patients with an index manic or hypomanic episode that had not been treated with study drug during the index episode ($p<0.01$) and also in patients with prior hypomanic but no manic episodes ($p<0.05$). Their dropout rate was similar in the two groups (36.4 % vs. 26 %). There was no difference between treatment arms in terms concerning the relapse into a mood episode when only completers were considered (36 % vs. 32 %). Overall the data suggested that lithium was found to be superior in prophylactic efficacy to carbamazepine in BD patients not previously treated with mood stabilizers (Hartong et al. 2003).

Overall the data suggest that there are no significant differences between lithium and carbamazepine. There might be some superiority of lithium in the treatment of more 'classic' patients, but in the rest of patients, the two agents were comparable.

Lithium Versus Valproate

The first comparison trial included 372 BD patients who met the recovery criteria within 3 months of the onset of an index manic episode. These patients were randomized to maintenance treatment with lithium (0.8–1.2 mmol/l; $N=91$),

divalproex (75–125 μg/ml; $N=372$) or placebo ($N=94$) for a period of 52 weeks. The patients should have been randomized within 3 months from the onset of the index episode, and they were required to be manic, partially recovered or remitted but not depressed at randomization. They were required to fulfil the inclusion criteria for two subsequent assessments, 6 days apart from each other. The three treatment groups did not differ concerning the time to manifestation of any mood episode, and this was also the case concerning manic or depressive episodes alone. Thus this is considered to be a failed study. The lithium group had higher rates of tremor, thirst and polyuria, while the divalproex group had higher rates of tremor, sedation, weight gain and reduction in platelet blood count (Bowden et al. 2000).

A second study investigated the efficacy of lithium vs. valproate in rapid cycling patients. That trial lasted 20 months and included 254 recently hypomanic/manic patients who had experienced a persistent bimodal response to combined treatment with lithium and divalproex. Only 60 patients remained after the open-label phase and were randomly assigned to lithium or divalproex monotherapy. The two agents had comparable efficacy in terms of relapse into any mood episode (56 % vs. 50 %), and this was also true both for depressive (34 % vs. 29 %) as well as for hypomanic/manic relapses (19 % vs. 22 %). There were no significant differences in time to relapse. More patients in the lithium group dropped out because of adverse events (16 % vs. 4 %) (Calabrese et al. 2005b).

Finally one study recruited 98 BD patients with a history of suicide attempts and assigned them to receive in a double-blind way lithium ($N=49$) or valproate ($N=49$) plus adjunctive medications as indicated for 2.5 years. Overall there were 45 suicide events in 35 participants (35.7 %), but no suicides. There were no differences between treatment groups in time to suicide attempt or to suicide event (Oquendo et al. 2011).

Again lithium was comparable to valproate in terms of prevention of mood episodes and suicidality.

Lithium Versus Lamotrigine

As mentioned before, three placebo-controlled RCTs suggested that at dosages of 50–400 mg daily, lamotrigine was comparable to lithium and superior to placebo at prolonging the time to intervention for any mood episode in BD-I patients who had recently experienced a manic or hypomanic episode. Lamotrigine was more efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic and mixed episodes. It is important that in these two RCTs patients received lamotrigine during the acute phase, thus suggesting that the study sample was not really enriched in favour of either compound, since lamotrigine is not efficacious during the acute phase (Bowden et al. 2003; Calabrese et al. 2003a).

Lithium Versus Antidepressants

There are three studies comparing lithium and antidepressants during the maintenance phase. In the first one, 122 patients with recurrent affective illness were randomly assigned to lithium, imipramine or placebo therapy for 2 years following discharge from hospitalization for acute depression. In bipolar patients lithium was

significantly more effective than imipramine or placebo in preventing any mood episode. Both treatments were significantly more effective than placebo. It is interesting that the difference between medication arms was due primarily to depressive episodes (Prien et al. 1973b). In the second one, 117 BD patients which received lithium carbonate or imipramine hydrochloride or both reported that lithium carbonate and the combination treatment were superior to imipramine in the prevention of manic recurrences and were as effective as imipramine in the preventing of depressive episodes. This was the first study to document that the efficacy of lithium might not include all phases of BD (Prien et al. 1984). The third one included 81 BD-II patients who recovered from their major depressive episode during initial open-label fluoxetine monotherapy that was randomly assigned to receive 50 weeks of double-blind monotherapy with fluoxetine (10–40 mg/day; $N=28$) or lithium (300–1,200 mg/day; $N=26$) or placebo ($N=27$). The mean time to relapse was significantly longer for fluoxetine (249.9 vs. 156.4 vs. 186.9 days). The estimated hazard of relapse was 2.5 times greater with lithium than with fluoxetine (Amsterdam and Shults 2010).

Thus the above studies suggest that lithium was superior to imipramine concerning the prevention of depression in BD-I patients but inferior to fluoxetine in BD-II patients.

Lithium Versus SGAs

There are two trials which compare lithium with an SGA. In the first one, acutely manic or mixed BD-I patients entered the study and received open-label co-treatment with olanzapine and lithium for 6–12 weeks. Those who remitted were randomly assigned to 52 weeks of double-blind monotherapy with olanzapine (5–20 mg/day; $N=217$) or lithium (target blood level: 0.6–1.2 meq/l; $N=214$). The two treatment groups had similar relapse rates (30 % vs. 38.8 %). There was some superiority of olanzapine in the prevention of manic or mixed episodes. The two agents did not differ concerning the prevention of depressive episodes. There was a significantly greater weight gain olanzapine than with lithium (1.8 kg vs. −1.4 kg) (Tohen et al. 2005). That study sample included patients in a manic/mixed episode and was possibly biased towards a manic/mixed predominant polarity. During the acute phase patients received a combination of lithium plus olanzapine, and no duration of response/remission was required in order to continue to the 'maintenance' phase.

The second study randomized manic or mixed BD-I patients to 12 weeks of lithium vs. aripiprazole monotherapy and those who responded to an additional 40-week maintenance (52 weeks total treatment). During this phase, patients continued receiving either aripiprazole (15 or 30 mg/day) or lithium (900, 1,200 or 1,500 mg/day). Of the 66 patients who entered the extension phase, only 20 patients (30.3 %) completed the entire phase (aripiprazole $N=7$; lithium $N=13$). The two agents appeared to be comparable. The most common treatment-emergent adverse events in the extension phase for aripiprazole were akathisia, headache, somnolence, anxiety and nasopharyngitis (all 8 %) and for lithium were insomnia (15.8 %), headache (13.2 %), diarrhoea (13.2 %) and vomiting (10.5 %) (El-Mallakh et al. 2012).

According to the above data, lithium was comparable to olanzapine and aripiprazole for the maintenance treatment of BD.

16.2.3.2.2 Valproate Versus Others

The studies concerning the comparison of valproate with lithium have already been discussed above (Bowden et al. 2000; Calabrese et al. 2005b; Oquendo et al. 2011).

Two trials compare valproate vs. olanzapine. The first one was a 47-week, randomized, double-blind study and compared olanzapine (5–20 mg/day) to divalproex (500–2,500 mg/day) in 251 BD-I patients in a manic or mixed episode. At endpoint there was no difference between the treatment groups in terms of mean improvement in YMRS score. The median time to symptomatic mania remission was significantly shorter for olanzapine (14 days vs. 62 days), but there were no significant differences between groups in the rates of symptomatic mania remission (56.8 % vs. 45.5 %) and subsequent relapse into mania or depression (42.3 % vs. 56.5 %). Treatment-emergent adverse events occurring significantly more frequently during olanzapine treatment were somnolence, dry mouth, increased appetite, weight gain, akathisia and high alanine aminotransferase levels; those for divalproex were nausea and nervousness (Tohen et al. 2003b). The cost analysis of the results of the previous study suggested that the overall per-patient treatment costs were similar for olanzapine and divalproex (Zhu et al. 2005).

16.2.3.2.3 Carbamazepine Versus Others

Carbamazepine has been studied only in comparison to lithium, and these studies have been discussed previously in the paragraph concerning lithium (Greil et al. 1997; Small et al. 1991; Kleindienst and Greil 2000, 2002; Hartong et al. 2003; Coxhead et al. 1992; Denicoff et al. 1997; Greil and Kleindienst 1999a; Placidi et al. 1986; Watkins et al. 1987; Lusznat et al. 1988; Simhandl et al. 1993).

16.2.3.2.4 Olanzapine Versus Others

The comparisons of olanzapine with lithium (Tohen et al. 2005) and valproate (Tohen et al. 2003b; Zhu et al. 2005) have been discussed above.

There is one study which compared olanzapine with asenapine, and it was an extension of the acute phase of an asenapine vs. olanzapine trial (McIntyre et al. 2009b). The extension phase included a 9-week double-blind extension followed by a 40-week double-blind extension. Patients entering the extension phase maintained their pre-established treatment, but those originally randomized to placebo received flexible-dose asenapine. Eventually all were receiving either flexible-dose asenapine (10–20 mg/day; $N = 111$) or olanzapine (5–20 mg/day; $N = 107$). At endpoint the change in the mean YMRS score was similar in the two groups (–28.2 vs. −28.6). Also the adverse events rate was similar between groups. The most frequent treatment-emergent AEs were insomnia, sedation and depression with asenapine and weight gain, somnolence and sedation with olanzapine (McIntyre et al. 2010a).

There is also only one study which compared olanzapine with paliperidone. It included 766 BD-I patients with current manic or mixed episodes (rapid cycling excluded) which were initially randomized to olanzapine (5–20 mg/day; $N = 149$) or

paliperidone ER (3–12 mg/day; $N=617$) for an acute treatment phase of 3-week duration. The responders continued the same treatment during a 12-week continuation phase, and those patients on paliperidone ER who achieved remission during this phase were randomized to fixed-dose paliperidone ER ($N=152$) or placebo ($N=148$), while those on olanzapine continued to receive that at fixed dose ($N=83$). This maintenance phase continued until at least 140 recurrences occurred among patients originally assigned to paliperidone ER in the acute treatment phase. The median time to recurrence of any mood symptoms was not observed with olanzapine (<50 % of patients experienced recurrence) and was significantly longer for paliperidone vs. placebo (558 vs. 283 days; $p=0.017$). Olanzapine-treated patients had significantly longer time to recurrence for any mood symptoms in comparison to either group ($p<0.001$). For paliperidone the difference was significant for preventing recurrence of manic, but not depressive symptoms. This clarification is not reported concerning olanzapine. Treatment-emergent adverse events occurred more often in olanzapine group (64 %) than placebo (59 %) or paliperidone ER groups (55 %) (Berwaerts et al. 2012a).

16.2.3.2.5 Other Comparisons

The comparison of aripiprazole (El-Mallakh et al. 2012), fluoxetine (Amsterdam and Shults 2010) imipramine (Prien et al. 1984) and lamotrigine (Bowden et al. 2003; Calabrese et al. 2003a) with lithium and of asenapine (McIntyre et al. 2010a) and paliperidone with olanzapine (Berwaerts et al. 2012a) has been discussed previously.

One 25-week RCT (expansion of an acute phase study (Brown et al. 2006) compared the olanzapine–fluoxetine combination (OFC 6/25, 6/50, 12/25 or 12/50 mg/day) vs. lamotrigine (titrated to 200 mg/day) in the prevention of bipolar depression in patients who responded to either the OFC or lamotrigine during the acute phase (note: the acute data are negative for lamotrigine vs. placebo). The results suggested that at endpoint patients with BD-I depression had significantly greater symptom improvement in terms of YMRS and MADRS scores on OFC compared with lamotrigine, but there was no treatment difference in the incidence of relapse. OFC-treated patients had more treatment-emergent adverse events and greater incidence of weight gain and hypercholesterolaemia. Thus, bipolar depressive patients who responded to OFC do better on long-term OFC in comparison to spontaneously improved patients on long-term lamotrigine (Brown et al. 2009).

Finally, there is one 6-week study which compared the efficacy of venlafaxine monotherapy (37.5–225 mg/day) in 15 women with BD-II vs. 17 women with unipolar (UP) depression years). The results suggested that the efficacy of venlafaxine was similar in the two treatment groups. No episodes of drug-induced hypomania or rapid cycling were observed (Amsterdam and Garcia-Espana 2000).

16.2.3.2.6 Summary of Comparison Studies

Overall the literature suggests that lithium is comparable with carbamazepine, valproate, olanzapine and aripiprazole. It might be more efficacious than carbamazepine in more ‘classic’ patients, but not less efficacious in the rest. Lamotrigine is

more efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic and mixed episodes. In the prevention of depressive episodes, lithium was shown to be superior to imipramine but inferior to fluoxetine in BD-II patients, while OFC has shown some superiority in comparison to lamotrigine. Valproate and olanzapine were shown to be comparable, which is in accord with their comparison with lithium separately. Olanzapine was shown to be comparable with asenapine but superior to paliperidone ER.

16.2.3.3 Combination and Add-On Treatment

A summary of combination and add-on treatment data for the maintenance phase is shown in Table 16.7.

16.2.3.3.1 Combination Treatment

There are three early studies which investigated the combination of lithium with another agent. All were negative, but the problems in their design limit the interpretation of the results. In the first combination treatment trial, 22 BD-II patients in remission for at least 6 months were randomly assigned to lithium, imipramine, lithium plus imipramine or placebo. The results suggested that lithium was efficacious in the prevention of relapse of any type, but imipramine was not efficacious either as monotherapy or in the combination group (Kane et al. 1982). In the second one, 117 BD patients received lithium, imipramine or both and reported that lithium and the combination treatment were superior to imipramine in the prevention of manic recurrences and were as effective as imipramine in the preventing of depressive episodes (Prien et al. 1984). In the third study, 52 outpatients with BD were randomized to receive lithium or carbamazepine, a crossover to the opposite drug in the second year, and then a third year on the combination. There was no difference between the treatment groups in terms of marked or moderate improvement (33.3 % vs. 31.4 % vs. 55.2 %). Lithium was superior to carbamazepine in the prophylaxis of mania. Patients with a past history of rapid cycling did poorly on monotherapy and better on combination treatment (28.0 % vs. 19.0 % vs. 56.3 %; $p<0.05$) (Denicoff et al. 1997).

The first study with a modern methodology took part in 2004 and was a 6-month maintenance study of lithium, carbamazepine or valproate plus perphenazine (4–64 mg/day; $N=18$) or placebo ($N=19$) in patients who had just remitted from an acute manic or mixed episode with or without psychotic features and retained remission for at least 2 weeks. The results suggested that patients receiving perphenazine had not had a better course in comparison to those receiving placebo, but on the contrary they had a shorter time to depressive relapse, more dropouts and have increased rates of dysphoria and depressive symptoms (Zarate and Tohen 2004).

One 18-month discontinuation placebo-controlled study included 99 BD-I patients who had achieved syndromic remission after 6 weeks of treatment with combination of olanzapine 5–20 mg/day plus lithium (0.6–1.2 mmol/l) or valproate (50–125 μg/ml). During the double-blind phase, patients were randomized to lithium or valproate plus olanzapine ($N=51$) or placebo ($N=48$). The results suggested that there was no difference between study groups in terms of syndromic relapse but was significant for symptomatic relapse (163 days vs. 42 days; $p=0.023$) (Tohen et al. 2004).

Another international study examined the efficacy and safety of quetiapine on lithium or divalproex in the prevention of mood episodes in BD-I patients with most recent episode manic/mixed or depressive. All patients received open-label quetiapine plus lithium or divalproex for up to 36 weeks to achieve at least 12 weeks of clinical stability. Then they were subsequently randomized to lithium (target serum concentrations 0.5–1.2 mEq/l) or divalproex (target serum concentrations 50–125 μg/ml) plus quetiapine (400–800 mg/day; $N=336$) or placebo ($N=367$) for up to 104 weeks. The results suggested that the combination significantly increased the time to recurrence of any mood event in comparison to placebo, and the relapse rate was lower in the combination group (18.5 % vs. 49.0 %). This beneficial effect concerned both manic and depressive episodes and corresponded to risk reductions >70 %. The combination was more efficacious than a mood stabilizer alone irrespective of index episode, mood stabilizer and rapid cycling status. During the randomization phase, there was an increase in weight of 0.5 kg in the quetiapine group and a reduction of 1.9 kg in the placebo group. More patients in the combination group manifested an elevation of serum glucose levels (Vieta et al. 2008b). There was a North American study with a similar design as the previous one (combination group $N=310$; placebo group $N=313$) and reported the same results with the international study (Suppes et al. 2009). These combination studies appear to be the first to report prevention on both depression and mania regardless of the type of index episode and rapid cycling status.

The OFC is a standard combination with proven efficacy against acute bipolar depression (Brown et al. 2006). There is one 25-week RCT (expansion of the acute phase study) which compared the OFC (6/25, 6/50, 12/25 or 12/50 mg/day) vs. lamotrigine (titrated to 200 mg/day) in the prevention of bipolar depression in patients who responded to either the OFC or lamotrigine during the acute phase (note: the acute data are negative for lamotrigine vs. placebo). The results suggested that at endpoint patients with BD-I depression had significantly greater symptom improvement in terms of YMRS and MADRS scores on OFC compared with lamotrigine, but there was no treatment difference in terms of incidence of relapse. OFC-treated patients had more treatment-emergent adverse events and greater incidence of weight gain and hypercholesterolaemia. Thus, bipolar depressive patients who responded to OFC do better on long-term OFC in comparison to spontaneously improved patients on long-term lamotrigine (Brown et al. 2009).

Another discontinuation 6-month RCT included 240 BD-I patients in an acute manic episode who responded to open-label ziprasidone plus a mood stabilizer and maintained response for at least eight consecutive weeks. These patients were randomized to receive either the combination of lithium or valproate plus ziprasidone (80–160 mg/day; $N=127$) or lithium or valproate alone ($N=113$). The results suggested that the combination was superior to mood stabilizer alone (relapse rate 19.7 % vs. 32.4 %; longer median time to intervention for the combination: 43.0 days vs. 26.5 days; $p=0.01$). Also the time to discontinuation for any reason was significantly longer for the combination arm ($p=0.0047$). Only tremor occurred more frequently in the combination arm (6.3 % vs. 3.6 %) (Bowden et al. 2010).

One open-label 24-month study (BALANCE trial) included 330 BD-I patients from 41 sites in the UK, France, USA and Italy and randomized them to lithium

monotherapy (plasma concentration 0.4–1.0 mmol/l, $N=110$), valproate monotherapy (750–1,250 mg, $N=110$) or both agents in combination ($N=110$), after an active run-in of 4–8 weeks on the combination. The results revealed that the combination group had less outcome events (59 % vs. 69 % vs. 54 %). The hazard ratios for the primary outcome were 0.59 ($p=0.0023$) for combination therapy vs. valproate, 0.82 ($p=0.27$) for combination therapy vs. lithium and 0.71 ($p=0.0472$) for lithium vs. valproate. It is important to note that 16 participants had serious adverse events after randomization. Of them seven were receiving valproate monotherapy (three deaths), five lithium monotherapy (two deaths) and four combination therapy (one death). Overall the results neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy, but clearly suggest that it is superior to valproate alone (Geddes et al. 2010). There are some methodological issues that might be responsible for these results at least partially (Fountoulakis 2010a).

A 24-week discontinuation trial of aripiprazole from Korea included 175 BD-I patients in a manic or mixed episode who were treated for 6 weeks with open-label divalproex plus aripiprazole. Stabilized patients for at least 2 weeks were randomized to 24 weeks of divalproex (50–125 μg/ml) plus aripiprazole (10–30 mg/day; $N=40$) or placebo ($N=43$). The results suggested that the time to relapse of any mood episode was similar in the two treatment groups ($p=0.098$). Weight gain was similar in the two groups and so were other adverse events (Woo et al. 2011).

One study included 787 BD-I patients with a recent manic or mixed episode (rapid cycling included) and applied a 9–24-week stabilization phase to them with single-blind aripiprazole (10–30 mg/day) plus open-label lamotrigine (100 or 200 mg/day). Of them 351 were stabilized for eight consecutive weeks and were randomized to aripiprazole plus lamotrigine ($N=178$) or placebo plus lamotrigine ($N=173$) and were followed-up for 52 weeks. At endpoint the two groups were not different in terms of time to any relapse, and this was also true concerning manic, mixed or depressive relapses although the combination group had a numerically longer time to relapse. Fewer patients in the combination group had relapsed at endpoint (11 % vs. 23 %) yielding a NNT of 9 (95 % CI: 5–121). The three most common adverse events in the combination group were akathisia, insomnia and anxiety (Carlson et al. 2012).

Another study included 164 recently depressed BD-I or BD-II patients, treated them with a combination of lamotrigine (up to 200 mg/day) plus divalproex (45–120 μg/ml or maximum daily dosage of 2,500 mg) and randomized those who were stabilized to 8 months of double-blind treatment with lamotrigine plus placebo ($N=45$) vs. lamotrigine plus divalproex ($N=41$). At endpoint the time to depressive episode did not differ significantly between groups (Bowden et al. 2012).

Overall, there is no compelling data that combination treatment in general does better than monotherapy. Most of the combination trials are negative and suggest that starting with monotherapy could be the best option for most patients. However for those patients stabilized on combination treatment, shifting them to monotherapy is the wrong choice. The exception is combination treatment with quetiapine or ziprasidone plus a mood stabilizer which according to the data might do better than

a mood stabilizer alone, and thus they might constitute the only combinations worth to start with from the beginning.

16.2.3.3.2 Add-On Treatment

The first add-on study was a randomized, open study of clozapine ($N=19$) as add-on therapy vs. treatment as usual ($N=19$) in patients with treatment-resistant BD or schizoaffective disorder who were followed up for 1 year. The results suggested the presence of significant clinical improvement in the clozapine group in comparison to treatment as usual (Suppes et al. 1999).

Another add-on study investigated the efficacy of phenytoin in 23 BD patients who had at least one episode per year in the previous 2 years despite ongoing prophylaxis but were stable for a mean of 4 months (range 1–13) before entering the study. Phenytoin or placebo was added to their current therapy in a double-blind crossover design for 6 months in each phase, leading to 30 observation periods of 6 months each. At the end of the study three patients on phenytoin and nine on placebo experienced a relapse, suggesting the presence of a significant prophylactic effect for phenytoin ($p=0.02$) (Mishory et al. 2003).

One small 1-year, double-blind, randomized, comparative, placebo-controlled, parallel-group, multicentre study investigated the efficacy of gabapentin ($N=13$) or placebo ($N=12$) added to the current treatment (lithium, valproate, carbamazepine or any combination but not antipsychotics or antidepressants) in euthymic BD-I or BD-II patients with at least two mood episodes during the last year. The results suggested that the combination was superior to placebo at endpoint in terms of change in the CGI-BP-Mania score (−2.1 vs. −0.6; $p=0.0046$). No emerging manic or depressive symptoms were seen in either group. The combination group manifested also a significant reduction in the use of sleeping medication (Vieta et al. 2006).

A 52-week, double-blind, randomized, placebo-controlled, parallel-group, multicentre, clinical trial included 55 BD-I and BD-II outpatients which had had two or more episodes during the last year, but currently being in remission and assigned them to oxcarbazepine ($N=26$) or placebo ($N=29$) as adjunctive treatment to ongoing therapy with lithium. Overall there was no difference between the treatment groups either in time to recurrence for any mood episode (19.2 vs. 18.6; $p=0.315$) or in the recurrence rates (38.46 % vs. 58.62 %; $p=0.135$). There was a trend for depressive episodes being less likely in the oxcarbazepine group (11.54 % vs. 31.03 %; $p=0.085$) and for better functionality with the GAF ($p=0.074$). The only significant finding concerned impulsivity was significantly better prevented by oxcarbazepine ($p=0.044$) (Vieta et al. 2008a).

One trial included 83 outpatients with bipolar depression and unsatisfactory response to treatment with lithium, valproate or carbamazepine and treated them for 10 weeks with the same mood stabilizer plus one of three double-blind randomly assigned antidepressants. Both the 61 patients who showed response as well as the 22 patients who showed partial response entered the 1-year double-blind continuation trial of their medication. At study endpoint, 42 (69 %) of the 61 acute positive responders maintained positive response and 32 (53 %) achieved remission. Only 6 (27 %) of the 22 acute partial responders had achieved positive treatment response at study endpoint.

Eight acute positive responders (13 %) and five acute partial responders (22 %) developed mania. These results suggest that patients who respond to treatment with mood stabilizers plus antidepressants maintain response with the same continued treatment; however, those patients who manifest only a partial acute response are unlikely to further improve when the same treatment is sustained (Altshuler et al. 2009).

The only large controlled trial which evaluated adjunctive maintenance treatment with a long-acting injectable antipsychotic in BD included 240 BD-I patients with at least four mood episodes in the 12 months prior to study entry. These patients entered a 16-week, open-label stabilization phase with RLAI plus TAU. Those who remitted ($N=124$) entered a 52-week, double-blind, placebo-controlled phase and were randomized to continued treatment with adjunctive RLAI (25–50 mg every 2 weeks) plus TAU ($N=65$) or to adjunctive placebo injection plus TAU ($N=59$). The time to relapse was longer ($p=0.010$), and the relapse rates were lower in patients receiving adjunctive RLAI (23.1 % vs. 45.8 % $p=0.011$). More patients under RLAI discontinued because of adverse events (4.6 % vs. 1.7 %). The most frequent adverse events related to RLAI treatment in comparison to placebo were tremor (24.6 % vs. 10.2 %), insomnia (20.0 % vs. 18.6 %), muscle rigidity (12.3 % vs. 5.1 %), increased weight (6.2 % vs. 1.7 %) and hypokinesia (7.7 % vs. 0.0 %) (Macfadden et al. 2009).

A recent complex trial included 124 bipolar depressed patients refractory to lithium. As previously discussed, these patients were randomized to addition of lamotrigine ($N=64$) or placebo ($n=60$) (van der Loos et al. 2009), and after 8 weeks, paroxetine was added to nonresponders for another 8 weeks ($N=27$) (van der Loos et al. 2010). The patients who responded ($N=65$, of them 25 under lithium plus lamotrigine, 5 under lithium plus lamotrigine plus paroxetine, 6 under paroxetine plus lithium and 19 under lithium monotherapy) continued medication and were followed for up to 68 weeks or until a relapse or recurrence of a depressive or manic episode. These authors compared the two groups defined by the presence of lamotrigine or not. The results suggested that although a numerical superiority in the time to relapse or recurrence was observed for the lamotrigine group vs. the other group (median time 10.0 vs. 3.5 months), this difference was not significant, and therefore these results do not support the authors' conclusion that the maintenance treatment with combination of lamotrigine plus lithium is superior to lithium alone. Furthermore, at study endpoint a similar percentage of patients was still in the study (28.1 % vs. 23.3 %) (van der Loos et al. 2011).

Another trial included 1,270 BD-I patients with a current manic or mixed episode and treated them with lithium or valproate for 2 weeks. Those with inadequate response ($N=686$) received adjunctive single-blind aripiprazole or placebo, and those patients who achieved stability for 12 consecutive weeks ($N=337$) were randomized to double-blind aripiprazole (10–30 mg/day; $N=168$) or placebo ($N=169$) on top of lithium or valproate for 52 weeks. Fewer patients in the aripiprazole group relapsed (17 % vs. 29 %; $p=0.014$). Also the aripiprazole group manifested significantly delayed time to any relapse compared to the placebo group. The significant difference concerned manic and mixed but not depressive relapses. The most common adverse events with adjunctive aripiprazole treatment were headache (13.2 %

vs. 10.8 %), weight increase (9.0 % vs. 6.6 %), tremor (6.0 % vs. 2.4 %) and insomnia (5.4 % vs. 9.6 %) (Marcus et al. 2011).

One study on 50 stable outpatients with BD-I or BD-II added pramipexole ($N=21$) or placebo ($N=24$) on TAU for 8 weeks. Although this is a short duration study, it could be considered to belong to the maintenance phase since it included stabilized patients. The primary cognitive analyses indicated no compelling cognitive benefit of pramipexole vs. placebo, although several methodological problems were present. The major issue was the presence of subsyndromal mood symptoms. In strictly euthymic patients pramipexole might had exerted a beneficial effect ($p=0.03$) (Burdick et al. 2012)

A 12-week study in 324 manic or mixed episodes with asenapine (5–10 mg; $N=158$) vs. placebo ($N=166$) on lithium or valproate reported that adjunctive asenapine significantly improved the YMRS score at week 3 and the response and remission rates at week 12. Those patients who completed this core study were eligible for a 40-week double-blind extension which however assessed only safety and tolerability, because only a small number of patients entered the extension. Treatment-emergent adverse events reported by 5 % or more of asenapine patients and at twice the incidence of placebo were sedation, somnolence, depressive symptoms, oral hypoesthesia and increased weight. Overall adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks (Szegedi et al. 2012).

The efficacy of 2 g/day N-acetyl cysteine (NAC) which is a glutathione precursor as adjunct maintenance treatment for BD was examined in 149 BD patients with MADRS score ≥12 at trial entry. After 8 weeks of open-label NAC treatment, they were randomized to adjunctive NAC or placebo, in addition to treatment as usual. Overall there were no significant between-group differences in recurrence or symptomatic outcomes during the maintenance phase of the trial (Berk et al. 2012).

Two trials investigated the efficacy of adjunctive N-acetyl cysteine (NAC). The first one randomized 75 BD patients during the maintenance phase and reported that NAC treatment caused a significant improvement on the MADRS score in comparison to placebo ($p=0.002$). Improvements were lost after washout. There was no effect of NAC on time to a mood episode and no significant between-group differences in adverse events (Berk et al. 2008). The second randomized 14 patients (not all of them with high depression scores) and reported a superiority of the NAC group vs. placebo in terms of remission ($p=0.031$) (Magalhaes et al. 2011). One maintenance study supported the usefulness of ramelteon in the prevention of relapse in BD patients (Norris et al. 2013).

There are some studies suggesting that there is a role for various nutritional supplements such as n-3 fatty acids, chromium, choline, magnesium and tryptophan alone or in combination with pharmacotherapies for the treatment of BD, but the data are of low quality (Sylvia et al. 2013).

16.2.3.4 Post Hoc Reviews and Meta-analytic Studies

16.2.3.4.1 Post Hoc Analyses

There are a number of post hoc analyses which shed some light on a number of questions. They are mentioned below in chronological order of publication.

A sub-analysis of the MAP study which subdivided the patients into 'classical' BD-I without mood-incongruent delusions and without comorbidity ($N=67$) and a nonclassical subgroup including all other patients ($N=104$) reported that the 'classical' group had a lower rehospitalization rate with lithium than with carbamazepine prophylaxis ($p=0.005$), while in the nonclassical group there was no difference between agents although a trend in favour of carbamazepine was found. An additional sub-analysis included mixed states as an additional nonclassical feature and confirmed the results (Greil et al. 1998).

Breakthrough depression is a common problem in the treatment of bipolar disorder. Only one, recently published, double-blind, placebo-controlled trial has examined the efficacy of divalproex in the prevention of depressive episodes in bipolar patients in the frame of an additional analysis of a previously mentioned trial (Bowden et al. 2000). That study lasted for 52 weeks after an index manic episode and randomized patients to maintenance treatment with divalproex ($N=187$), lithium ($N=91$) or placebo ($N=94$) plus adjunctive paroxetine or sertraline for breakthrough depression. The results of the additional analysis suggested that the discontinuation rate for any reason was lower among patients in the divalproex group taking an SSRI than among patients in the placebo group taking an SSRI (56 % vs. 85 %; $p=0.043$) (Gyulai et al. 2003b).

The post hoc analysis of a 24-week, double-blind, placebo-controlled study of ziprasidone or placebo plus lithium or valproate (Bowden et al. 2010) with the utilization of four different remission criteria suggested that the application of different definitions of remission does not make any significant difference concerning the results (Pae et al. 2012).

Another post hoc analysis investigated the response of symptoms associated with suicidality in BD-I patients and assessed the suicide risk during treatment with olanzapine in combination with lithium or divalproex. It utilized data from a previously published trial (Tohen et al. 2004), in which manic or mixed-episode patients who were partially responsive to at least 2 weeks of lithium or divalproex monotherapy prior to study entry were randomly assigned to augmentation therapy with olanzapine (5–20 mg/day) or placebo. That study reported that patients taking olanzapine added to lithium or valproate experienced sustained symptomatic remission, but not syndromic remission, for longer than those receiving lithium or valproate monotherapy. The results of the post hoc analysis suggested that suicidality in adult, mixed-episode, BD-I disorder patients was associated with somatic discomfort, agitated depression and psychosis and that the addition of an atypical antipsychotic–antimanic agent in some BD patients might help to reduce suicidal ideation (Houston et al. 2006).

Another analysis suggested that using olanzapine early in the course of the disorder is possibly more beneficial than lithium during the maintenance phase. This study was a post hoc analysis of data from a multicentre, double-blind, 12-month maintenance trial in 431 BD-I initially euthymic patients with at least two prior manic/mixed episodes which were randomly assigned to olanzapine (5–20 mg/day) or lithium (serum concentration 0.6–1.2 mEq/l) (Tohen et al. 2005). The post hoc analysis subcategorized the patients by illness stage according to number of prior

manic/mixed episodes, early stage, 2 prior episodes ($N=53$, lithium; $N=48$, olanzapine); intermediate stage, 3–5 prior episodes ($N=80$, lithium; $N=98$, olanzapine); and later stage, more than 5 prior episodes ($N=81$, lithium; $N=71$, olanzapine), and reported that there were significant effects for treatment ($p<0.001$) and illness stage ($p=0.006$) but no significant interaction ($p=0.107$) on rate of manic/mixed relapse/recurrence. The rates for a manic or mixed relapse or recurrence for olanzapine vs. lithium were 2.1 % vs. 26.4 % ($p=0.008$), 13.3 % vs. 23.8 % ($p=0.073$) and 23.9 % vs. 33.3 % ($p=0.204$) for early-, intermediate- and later-stage groups, respectively. There was no significant effect for treatment ($p=0.096$) or illness stage ($p=0.731$) for depressive relapse or recurrence. These authors concluded that olanzapine maintenance therapy may be particularly effective early in the course of BD (Ketter et al. 2006).

Post hoc analyses were conducted on data from patients presenting with a mixed index episode who were enrolled in a larger maintenance trial of olanzapine vs. placebo for 48 weeks (Tohen et al. 2006). The original study included 731 BD patients, and of them 304 were suffering from an acute mixed episode (41.6 %). Of them, a total of 121 (39.8 %) remitted after the open-label phase and were randomized to olanzapine ($N=76$) or placebo ($N=45$). Compared to the placebo group, the olanzapine group had a lower incidence of 59.2 % vs. 91.1 %; $p<0.001$ and a longer time (46 vs. 15 days; $p<0.001$) to symptomatic relapse of any kind. This was true both for depressive symptomatic relapse (85 vs. 22 days; $p=0.001$) and manic symptomatic relapse (too few relapses to calculate vs. 42 days; $p<0.001$) (Tohen et al. 2009).

A post hoc analysis of a double-blind trial in which BD-I patients who had achieved stabilization from a manic, depressive or mixed episode during open-label treatment with quetiapine were randomized to continue quetiapine or to switch to lithium or placebo for up to 104 weeks (Weisler et al. 2011) reported that of patients randomized to lithium, 201 (59.5 %) obtained lithium levels between 0.6 and 1.2 mEq/l, and 137 (40.5 %) obtained lithium levels <0.6 mEq/l. Their outcomes were compared with those of patients receiving placebo ($N=404$), and the results suggested that the times to recurrence of any mood episode as well as a manic or depressive episode separately were significantly longer for the lithium 0.6–1.2 mEq/l group vs. placebo and vs. lithium <0.6 mEq/l, with no differences between lithium <0.6 mEq/l and placebo (Nolen and Weisler 2013).

Two clinical trials, prospectively designed for combined analysis, compared lithium and lamotrigine vs. placebo for the treatment of BD-I disorder in recently depressed or manic patients (Bowden et al. 2003; Calabrese et al. 2003a). Together they included 1,315 BD-I patients of which 638 were stabilized during the open-label phase and randomly assigned to double-blind monotherapy with lamotrigine (50–400 mg/day fixed dose or 100–400 mg/day flexible dose; $N=280$;), lithium (serum level of 0.8–1.1 mEq/l; $N=167$) or placebo ($N=191$) for 18 months. The results suggested that both lamotrigine and lithium were superior to placebo for time to intervention for any mood episode (197 vs. 184 vs. 86 days). Lamotrigine was superior to placebo for time to intervention for both mania and depression, and lithium was superior to placebo only concerning the time to intervention for mania.

Additional analyses adjusted for index mood did not change the results (Goodwin et al. 2004; Calabrese et al. 2003b). Both lamotrigine and lithium were more effective than placebo in delaying the time to intervention for any mood episode when relapses that occurred in the first 90 or 180 days were excluded from the analyses (Calabrese et al. 2006). A fourth post hoc analysis suggested that the lithium-induced thyroid function abnormalities could be partially responsible for its failure to prevent depression. The analysis showed that patients for whom lithium was ineffective in the prevention of depressive episodes had a significantly higher adjusted mean TSH level in comparison to those for whom lithium was successful (4.4 microIU/ml vs. 2.4 microIU/ml) (Frye et al. 2009). A fifth post hoc analysis of the same two trials focused on subsyndromal symptoms. It reported that significantly more patients under lamotrigine but not under lithium were in remission in comparison to placebo (63 % vs. 60 % vs. 53 %; $p=0.02$ and $p=0.165$, respectively). The median time to onset of subsyndromal symptoms was significantly longer in both treatment groups in comparison to placebo (15 vs. 15 vs. 9 days; $p<0.05$), and this was also true concerning the duration from onset of subsyndromal symptoms to subsequent mood episode (Frye et al. 2006). Finally, aripiprazole maintenance treatment as adjunctive on lithium or valproate is efficacious for a manic but not for a mixed index episode (Yatham et al. 2013).

16.2.3.4.2 Review and Meta-analyses

One review confirmed the efficacy of lithium but reported that there is no definitive evidence as to whether or not lithium has an anti-suicidal effect (Burgess et al. 2001). Two others supported the usefulness of RLAI (Bobo and Shelton 2010) and that of ziprasidone for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate (Citrome 2010). One review on the usefulness of aripiprazole in the maintenance phase of BD identified two publications, both describing the results of a single trial. It also identified four issues that the authors suggested they limit the interpretation of that trial (insufficient duration, enriched sample, possible conflation of iatrogenic adverse effects of abrupt medication discontinuation with beneficial effects of treatment and a low overall completion rate). They also stressed that the literature rarely mentions these limitations (Tsai et al. 2011). It should be mentioned however that these limitations are present in most maintenance trials and are valid for almost all agents. A number of papers discussed the place of aripiprazole in the treatment of BD (Goodwin et al. 2011; Sayyaparaju et al. 2014).

Concerning meta-analysis, the first one included four RCTs and failed to prove the prophylactic efficacy of carbamazepine (Dardennes et al. 1995). A second one on the usefulness of oxcarbazepine in the maintenance treatment of BD concluded that the data are of low quality and the evidence base is not sufficiently rigorous in terms of methodology to provide guidance on the use of oxcarbazepine in the maintenance treatment of BD (Vasudev et al. 2008).

A number of meta-analyses had focused on lithium. One of them analysed 19 lithium trials (865 patients) and found lithium highly efficacious in terms or recurrence prevention in comparison to placebo (29 % vs. 74 %). However it failed to

find sufficient evidence to prove that the lithium-withdrawal relapse phenomenon really exists (Davis et al. 1999). A more recent study included 22 lithium studies (5,647 patients; 33,473 patient-years of risk) and showed that suicide was 82 % less frequent during periods of treatment with lithium (Tondo et al. 2001). The presumed selectivity of lithium against mania was suggested to be a biased result caused by the discontinuation design of many studies, since discontinuation seems to predispose more to mania than depression (Burgess et al. 2001), but a more recent meta-analysis of 5 RCTs (with 770 participants) reported that lithium is especially strong concerning manic relapse prevention, while in the prevention of depressive relapses, it was found to be less potent, but still efficacious (Geddes et al. 2004).

A number of meta-analytic studies confirmed the antimanic efficacy of specific agents and the antidepressant of others. A systematic review and meta-analysis of 34 randomized and quasi-randomized controlled trials suggested that there is evidence for the efficacy of lithium, valproate and lamotrigine as maintenance therapy for the prevention of relapse in BD. Three drugs have a significant effect in the prevention of manic relapses (lithium, olanzapine and aripiprazole) and three in the prevention of depressive symptoms (valproate, lamotrigine and imipramine) (Beynon et al. 2009). Another one confirmed the efficacy of olanzapine in the prevention of mania but questioned its efficacy in the preventing of depressive relapses. It also pointed out that this efficacy was restricted to patients who have responded to olanzapine during the acute manic or mixed episode and who have not previously had a satisfactory response to lithium or valproate (Cipriani et al. 2010). Finally, the analysis of maintenance data from 15 studies reported that quetiapine, lithium, RLAI, aripiprazole and olanzapine were proven effective in manic recurrence prevention, while lamotrigine, quetiapine and lithium were proven effective also for the prevention of depressive relapses (Popovic et al. 2010).

Two analyses investigated combination treatment and both questioned its efficacy. The first reported that there is little evidence to support the efficacy of combination therapy (Beynon et al. 2009), while the second utilized data from 7 trials with a total of 350 BD patients. It reported that those long-term treatments that included antidepressants yielded 27 % lower risk of a depressive relapse in comparison to mood stabilizer alone or to no treatment. However the presence of an antidepressant was related with a 72 % greater risk for a manic relapse. The risk ratio was not significant in either case; therefore, these authors suggested that long-term adjunctive antidepressant treatment was not superior to a mood stabilizer alone (Ghaemi et al. 2008).

One final meta-analysis included 20 trials (5,364 patients). It confirmed that the majority of studies included samples enriched for response to a specific agent during the acute phase. The results suggested that no monotherapy was associated with a significantly reduced risk for both manic/mixed and depressed relapse. Of the combination treatments, only quetiapine + lithium/divalproex was associated with a significantly reduced risk vs. comparator (placebo + lithium/valproate) for relapse at both the manic/mixed and depressed poles of bipolar illness. Other limitations for the analysis and interpretation include differences in study durations and definitions of relapse (Vieta et al. 2011).

16.2.4 Treatment of Mixed Episodes

Mixed episodes are no longer accepted as a diagnostic entity by DSM-5; instead 'mixed features' is included as a specifier. The two concepts are significantly different, and the results concerning mixed episodes from the clinical trials so far cannot be applied directly in patients with this specifier. It is important to note that in clinical trials, mixed episodes are treated together with manic episodes. Some studies report the results concerning mixed episodes separately; however, they always concern trials of acute mania. No data on mixed episodes are reported in clinical trials of bipolar depression. An important limitation is the fact that in most studies, even when results are reported separately for mixed patients, they usually concern the manic but not the depressive component of the clinical picture (Fountoulakis et al. 2012d).

A summary of the data for the treatment of mixed episodes is shown in Table 16.8.

16.2.4.1 Treatment of Acute Mixed Episodes

Aripiprazole was reported to be efficacious in the treatment of acute mixed episodes, and this efficacy concerned both the manic and the depressive component. Additionally, the efficacy against the manic component was independent from the severity of the depressive component (Suppes et al. 2008a; Sachs et al. 2006; Keck et al. 2003b).

Asenapine is reported not to be efficacious against the manic component, but no data exist concerning the depressive component (McIntyre et al. 2009c). Olanzapine was reported to be efficacious against the manic, but the data are inconclusive concerning the depressive component (there might be some efficacy in the most severe cases and in specific subgroups) (McIntyre et al. 2009c; Tohen et al. 1999, 2000; Baldessarini et al. 2003; Baker et al. 2003; Shi et al. 2004b). Paliperidone is efficacious against the manic but not against the depressive component (Berwaerts et al. 2010; Vieta et al. 2010a). Risperidone is reported to be efficacious against the manic component, but it is unknown whether this is also true for the depressive component (Khanna et al. 2005). Ziprasidone is reported to be efficacious against both the manic and the depressive component, but this was reported in mixed states not similar to the DSM definition (Keck et al. 2003b; Potkin et al. 2005; Stahl et al. 2010; McElroy et al. 1992). Carbamazepine is efficacious both against the manic and against the depressive component (Weisler et al. 2004, 2005, 2006). Valproate is efficacious against the manic component, but the data concerning the depressive component are inconclusive (Bowden et al. 2006; Ghaemi et al. 2007).

In mixed depression, the OFC was comparable to olanzapine, and both were superior to placebo, but the report does not permit to derive conclusions (Benazzi et al. 2009; Tohen et al. 2003c).

The data concerning the combination of haloperidol or risperidone plus lithium or valproate were negative (Sachs et al. 2002), while the combinations of olanzapine plus lithium or valproate have positive data concerning both components (Tohen et al. 2002b; Baker et al. 2004; Houston et al. 2006, 2009, 2011). Overall it seems that SGAs are effective in the treatment of acute mixed episodes of BD, with

predominant manic symptoms. Their efficacy in treating depressed mixed episodes remains unclear (Muralidharan et al. 2013).

16.2.4.2 Maintenance Treatment of Mixed Bipolar Episodes

The data so far suggest that olanzapine prolongs relapse into any episode in patients with an index mixed episode (Tohen et al. 2006, 2009), while lithium and valproate had negative results in patients with a dysphoric manic index episode (Bowden et al. 2005a). The data are in support of the combination of quetiapine plus lithium or valproate (Vieta et al. 2008b; Suppes et al. 2009) but are negative concerning aripiprazole in patients with an index mixed episode (Yatham et al. 2013).

16.2.5 Treatment of Rapid Cycling Patients

The treatment of rapid cycling patients constitutes a challenge. Often their course frustrates the therapist, and the evaluation of treatment is difficult because of the rapid switching from one pole to another. Careful registration and evaluation of the long-term course is necessary in order to verify whether the overall frequency and/or severity of episodes improved (Fountoulakis et al. 2013a).

A summary of the data for the treatment of rapid cycling patients specifically for acute mania is shown in Table 16.8 and for acute bipolar depression is shown in Table 16.9.

16.2.5.1 Treatment of Acute Episodes in Rapid Cycling Patients

The secondary analysis of the data from a trial of olanzapine in acute mania suggested that olanzapine was effective in the reducing of the symptoms of mania and was well tolerated in rapid cycling BD-I patients (Sanger et al. 2003). The pooling of data from two RCTs reported that improvement of mania with olanzapine was similar in rapid cyclers and non-rapid cyclers. However, rapid cyclers showed an earlier response (Vieta et al. 2004). One trial was also positive concerning aripiprazole in acutely manic patients (Sachs et al. 2006).

Although one study on acute mania in rapid cycling patients was negative (Cutler et al. 2011), one a priori planned sub-analysis of data from rapid cycling patients with acute BD-I or BD-II depression suggested that quetiapine monotherapy (300–600 mg/day) was effective and well tolerated (Vieta et al. 2007). This was also confirmed by the post hoc analysis of the rapid cycling subsample of bipolar depressives from the BOLDER study (Cookson et al. 2007). Finally the sub-analysis of the data from a small number of depressed rapid cycling BD patients again suggested that 300 mg of quetiapine monotherapy was superior to placebo (Suppes et al. 2010).

Additionally there is some weak but positive signal for lithium (Young et al. 2010) and some positive but equivocal data for valproate (Muzina et al. 2010); however, the results are clearly negative for paroxetine (McElroy et al. 2010c).

The combination of lithium and divalproex is probably not effective, and the further addition of lamotrigine does not seem to add anything in terms of efficacy (Kemp et al. 2012a).

16.2.5.2 Relapse Prevention in Rapid Cycling Patients

The treatment during the maintenance phase and the relapse prevention is the most challenging aspect of the treatment of rapid cycling BD patients.

The data so far suggest that divalproex was not more effective than lithium (Calabrese et al. 2005b) and also the combination of lithium plus divalproex was not better than lithium alone (Kemp et al. 2009). However the combination of lithium plus carbamazepine did better than either agent alone, but the study sample of that trial was very small (Denicoff et al. 1997). The data are negative for lamotrigine although in some secondary outcomes there was a beneficial signal especially in BD-II patients (Calabrese et al. 2000). It is interesting to note that the popular concept among clinicians that divalproex is more effective than lithium in the long-term management of rapid cycling bipolar disorder was not supported by a trial on 139 patients (Findling et al. 2005).

In patients who continued open-label olanzapine therapy for 1 year after 3 weeks of double-blind therapy for acute mania, non-rapid cyclers were more likely to experience a symptomatic remission and were less likely to experience a recurrence, especially into a depressive phase. They also were less likely to be hospitalized and to make a suicide attempt (Vieta et al. 2004).

One post hoc analysis suggested that aripiprazole was efficacious (Muzina et al. 2008). There are no data on monotherapy with other antipsychotics concerning the maintenance phase. Another post hoc analysis reported that rapid cycling patients did less well during the extended observation period than non-rapid cycling patients, regardless of treatment, and that overall olanzapine and divalproex appeared comparable (Suppes et al. 2005).

An international study confirmed the efficacy and safety of quetiapine on lithium or divalproex in the prevention of mood episodes in rapid cycling BD-I patients with most recent episode being manic/mixed or depressive (Vieta et al. 2008b). There was a North American study with a similar design as the previous one and reported the same results (Suppes et al. 2009). A large controlled trial which evaluated adjunctive maintenance treatment with RLAI on TAU in 240 BD-I patients with at least four mood episodes in the 12 months prior to study entry returned positive results. These patients did not correspond exactly to the 'rapid cycling' definition; however, the results of the study are relevant for consideration in the treatment of rapid cycling patients (Macfadden et al. 2009).

Data from the STEP-BD support the role of antidepressants in the development of rapid cycling. A rapid cycling course predicted three times more depressive episodes in spite of continuation treatment with antidepressants. However, the study sample was very small (Ghaemi et al. 2010). Again according to the STEP-BD data, during follow-up, antidepressant use was associated with more frequent mood episodes (Schneck et al. 2008). A similar conclusion came from an earlier randomized controlled study of rapid cycling patients which utilized a double-blind on-off-on-off design with the use of tricyclic antidepressants (Wehr et al. 1988).

Finally, the data are negative concerning the administration of ethyl-eicosapentaenoate (EPA) 6 g/day as augmentation on ongoing treatment with mood stabilizers in rapid cycling patients with acute bipolar depression (Keck et al. 2006b).

One meta analysis suggested that lithium was at least partially efficacious in rapid cycling patients (Kupka et al. 2003), and another one suggested there is no clear advantage of any treatment option vs. the others (Tondo et al. 2003), while a third one found that some atypical antipsychotics (especially quetiapine and olanzapine) could be considered as the first-line treatment option (Cruz et al. 2010). The meta-analysis of 20 studies published from 1974 to 2002 comparing subjects with rapid and non-rapid cycling BD reported that in contrast to common beliefs, lithium prophylaxis had at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants were avoided. It should be mentioned however that hypothyroidism, which is a frequent adverse effect of lithium, might be associated with mood destabilization in vulnerable patients (Kupka et al. 2003).

16.2.6 Treatment of Special Conditions

16.2.6.1 Treatment of Comorbid Conditions

Comorbidity is a significant issue in bipolar patients and often needs specific therapeutic intervention. Simply adding medication might not be the correct strategy, at least not always.

16.2.6.1.1 Treatment of Comorbid Substance Abuse Disorder (SUD)

As shown in Chap. 9 of the current book, substance use, abuse and dependence is not uncommon in BD patients. Their coexistence perplexes the treatment for both conditions. Unfortunately, the data concerning the pharmacological treatment of substance use in patients with BD are limited.

There are two placebo-controlled trials suggesting that the combination of valproate and lithium in BD patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms and that lithium treatment in BD adolescents improves both mood and substance use symptoms (Cerullo and Strakowski 2007). Lithium can be used for the treatment of concomitant substance and polysubstance abuse (Geller et al. 1992, 1998), and quetiapine and risperidone can reduce drug craving (Nejtek et al. 2008). However, the data concerning quetiapine for alcohol abuse are negative (Brown et al. 2008). For bipolar patients with alcohol dependence, naltrexone could be useful (Sherwood Brown et al. 2009), and a preliminary report is positive for acamprosate (Tolliver et al. 2012).

There are open-label medication trials which provide limited support to quetiapine, aripiprazole and lamotrigine for the treatment of BD patients with cocaine dependence. Also, aripiprazole might be helpful in patients with alcohol use disorders (Cerullo and Strakowski 2007).

It is important to mention that during treatment with antidepressants, the presence of substance use might increase the risk of switching (Goldberg and Whiteside 2002).

In spite of the magnitude of the problem and the resulting disability, burden and cost, the existing data are insufficient to support an informed design of pharmaceutical treatment strategy in BD patients with SUD. Some data are available for alcohol,

cannabis and cocaine use comorbid with BD, but the literature is poor concerning heroin, amphetamine, methamphetamine and poly-SUD comorbid with BD (Beaulieu et al. 2012).

16.2.6.1.2 Treatment of Comorbid Anxiety and Anxiety Disorders

A post hoc analysis of anxiety symptoms with data from two RCTs (Calabrese et al. 2005a; Thase et al. 2006) of 8-week duration concerning quetiapine (300 or 600 mg/day) reported that at endpoint there was no difference between treatment groups and placebo concerning the total HAM-A score, but there was concerning both the psychic and somatic anxiety subscale scores in comparison with placebo ($p<0.001$). The baseline severity of anxiety did not impact the improvement in depressive symptoms (Lydiard et al. 2009). Also, quetiapine XR (50–300 mg/day) was superior both to divalproex ER (500–3,000 mg/day) and to placebo in the improvement of anxiety in BD patients with comorbid panic attack or GAD (Sheehan et al. 2013). In another study, again quetiapine (300 or 600 mg/day) and paroxetine (20 mg/day) produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline in acutely depressed BD patients (McElroy et al. 2010c). Finally, quetiapine (300–600 mg/day) significantly improved the HAM-A score from baseline, while this was not the case with lithium (600–1,800 mg/day; $p=0.279$) (Young et al. 2010).

Also lurasidone (20–60 mg/day; $N=166$ or 80–120 mg/day) significantly improved anxiety symptoms in comparison to placebo (Loebel et al. 2013).

On the contrary, risperidone monotherapy was not an effective anxiolytic for BD patients with comorbid panic disorder or GAD in doses of 0.5–4 mg/day over 8 weeks of treatment (Sheehan et al. 2009). As mentioned previously, negative were also the data concerning lithium (600–1,800 mg/day; $p=0.279$) (Young et al. 2010).

The data concerning divalproex (rapidly titrated up to 2,500 mg/day, as tolerated, to a target serum level of 50–100 mg/dl) are equivocal because the only positive study was based on a small study sample (25 outpatients with BD-I depression) (Davis et al. 2005).

It is reasonable to suggest that also benzodiazepines can be used as adjunctive medication for sedation or for the treatment of anxiety, although abuse, tolerance and dependence constitute important problems. Although approved for the treatment of GAD, pregabalin has no data on BD. However, again it is reasonable to suggest it might be a useful agent for the treatment of anxiety disorders that commonly accompany BD and could substitute for benzodiazepines, according to the clinical judgement of the therapist. A significant advantage is that it is not metabolized in the liver.

A summary of the data for the treatment of anxiety mostly during a bipolar depressive episode is shown in Table 16.9.

16.2.6.1.3 Weight Gain

Weight gain and the metabolic syndrome in general constitute a significant public health problem which is especially important in psychiatric patients.

Although the general approach is that lifestyle modifications are the main tool to control and even avoid weight gain, such approaches are of limited value in

psychiatric populations, who find it difficult to discipline concerning food intake and lack motivation to exercise. Therefore, besides the psychoeducation to push a change in lifestyle, a number of medications have been proposed as useful to tackle this problem.

Topiramate is not effective in the treatment of BD per se; however, it is unique because of its ability to cause weight loss at dosages of 50–200 mg/day. A review reported that more than 70 % of patients taking topiramate for a mean duration of 5 months lost a mean of 5–6 kg (Arnone 2005). The problem is that most agents with proven efficacy in weight loss might cause depression de novo, and topiramate itself could induce suicidality in some patients although no completed suicides related to topiramate have been reported (Fountoulakis et al. 2012a).

16.2.6.1.4 Treatment of Agitation

Agitation constitutes an important clinical problem which perplexes treatment. It is mostly present during the acute phase, both manic and depressive, but milder forms could be present during all phases of the illness. When severe, it often affects insight and interferes with proper treatment, and it usually demands specialized treatment itself.

A number of treatments have been proposed, but most are not studied adequately due to a number of methodological issues, including the obtaining of informed consent from the side of the patient. Probably most clinicians choose antipsychotics in their everyday clinical practice, and this option is supported by a double-blind clinical trial which reported that intramuscular haloperidol (5–10 mg) was equal in efficacy but faster acting in comparison to intramuscular clonazepam (1–2 mg) in agitated mania at 0, 30 and 60 min (Chouinard et al. 1993). Similarly, intramuscular olanzapine (10 mg, first two injections; 5 mg, third injection) was reported to be superior to lorazepam (2 mg, first two injections; 1 mg, third injection), for the controlling of agitation in manic patients. Already 2 h after the first injection, patients treated with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam (Meehan et al. 2001).

Valproate oral loading of 20 mg/kg/day was reported to be comparable to haloperidol 0.2 mg/kg/day for the treatment of excited manic patients in a single-blind study, and the effect was evident within 3 days from starting (McElroy et al. 1996). Overall, valproate loading up to 30 mg/kg/day was reported to be safe and well tolerated (Hirschfeld et al. 1999).

The most recent addition in the armamentarium for the treatment of acute agitation concerned the development of inhaled loxapine which could be considered as not as invasive as injections but still faster acting in comparison to oral formulas. One clinical trial was conducted in BD-I patients with agitation associated with manic or mixed episodes. The anti-agitation effect was observed at 10 min (first time point measured) for both the 5 mg and 10 mg doses. Loxapine remained superior to placebo throughout the remainder of the study at all time points measured. The effect size was comparable to what has been previously reported for intramuscular antipsychotics and benzodiazepines. For safety reasons it has been

recommended that inhaled loxapine be restricted to a single dose in 24 h and be subject to a Risk Evaluation and Mitigation Strategy programme (Citrome 2012; Kwentus et al. 2012).

16.2.6.1.5 Treatment of the Neurocognitive Deficit

One study compared pramipexole ($N=21$) vs. placebo ($N=24$) for the treatment of the neurocognitive deficit in stable BD-I or BD-II outpatients. Overall the two groups showed similar effect on neurocognitive function, but there was some efficacy for pramipexole in euthymic patients only (Burdick et al. 2012). Similarly, a trial which utilized N-acetyl cysteine (NAC) failed to support its efficacy for the improvement of neurocognitive function in BD patients (Dean et al. 2012).

On the contrary there are some data supporting the usefulness of insulin and mifepristone. In one study, euthymic BD patients were randomized to receive adjunctive intranasal insulin (40 IU q.i.d.; $N=34$) or placebo ($N=28$) for 8 weeks. A significant improvement vs. placebo was noted with intranasal insulin therapy on executive function but not on the other neurocognitive measures (McIntyre et al. 2012). The data were more robust concerning the effect of 600 mg/day of mifepristone (a synthetic steroid compound with both antiprogesterone and antiglucocorticoid properties) vs. placebo as an adjunctive treatment, for 1 week, in 60 patients with bipolar depression. Mifepristone improved the primary outcome which was spatial working memory, and this was evident 7 weeks after the cessation of treatment. The magnitude of this neuropsychological response was predicted by the magnitude of the cortisol response to mifepristone, but it was unrelated with the change in depressed mood (Watson et al. 2012).

16.2.6.1.6 Suicide

Suicide is not an uncommon outcome in the course of BD (see Chap. 19), and there is much discussion concerning the potential anti-suicidal efficacy of specific drugs and especially of lithium. However almost all the data come from studies of naturalistic and epidemiological nature, and no controlled studies exist.

There is only one post hoc analysis which investigated suicidality in BD-I patients during treatment with olanzapine in combination with lithium or divalproex. In mixed patients with residual suicidality, suicidal thoughts were associated with somatic discomfort, agitated depression and psychosis. It seems that combination therapy with olanzapine plus lithium ($N=36$) vs. lithium alone ($N=22$) differentially reduced the score in the suicidal item of the HAM-D by 58 % vs. 29 % ($p<0.05$) within 1 week and all associated symptoms within 2 weeks by averages of 31 % vs. 12 % ($p<0.05$) (Houston et al. 2006).

16.2.7 Cautions for Pharmaceutical Treatment in BD Patients

There are a number of issues that need attention during the treatment of BD with medication. It is well known that lithium has a narrow therapeutic window concerning its dosage and plasma levels (recommended plasma level 0.6–1.2 mmol/l).

Although the research data suggest it is well accepted with a good tolerability profile, often in clinical practice patients are dissatisfied because of sedation and tremor, and sometimes a decline in creative thinking is reported (see Chap. 20), although in patients under long-term lithium treatment, no further decline of neurocognitive function was observed (Engelsmann et al. 1988). Adverse events are more frequent with higher doses, while 'rebound mania' has been described on withdrawal. Additional drawbacks with lithium therapy also include laboratory testing and thorough investigation before starting treatment (ECG, kidney function, etc.), which often delay the initiation of treatment and disappoint the patient. It seems that overall fewer than 20 % of patients have no adverse effects at all, but also only about 30 % have more than minor complaints. The most frequent adverse events include neurological, endocrinological (more often from the thyroid), cardiovascular, renal, gastrointestinal, haematological and dermatological manifestations, while also lithium intoxication is not rare. It seems there is a complex relationship between lithium treatment, female gender, hypothyroidism and rapid cycling (Bauer and Whybrow 1990; Cowdry et al. 1983; Fountoulakis et al. 2008c; Bauer et al. 1990; Gyulai et al. 2003a). While most authors argue that lithium is neuroprotective, a neurotoxic effect is also possible in the long term, even at therapeutic levels, especially in combination with antipsychotics (Fountoulakis et al. 2008c). It is reported also that lithium plasma levels peak during the summer (Cusin et al. 2002; Wilting et al. 2007), especially in males (D'Mello et al. 1995), and this difference could be up to 25 % (Medhi et al. 2008).

As mentioned above, it is very interesting and well known that many patients under lithium complain that treatment inhibits their creativity and productivity (Shaw et al. 1986). It is important to note that this loss of creativity might be specifically related to lithium and not divalproex (Stoll et al. 1996) although there are studies rejecting this (Schou 1979). Overall it seems that patients are more creative when well stabilized and their symptoms are under good control (see Chap. 20). At any case, fortunately, cognitive complaints do not seem to be significant predictors of discontinuation of lithium treatment (Connelly et al. 1982; Maarbjerg et al. 1988). Apart from reduced creativity, a general negative impact of lithium on neurocognitive function has been reported, especially on memory and psychomotor functioning (Squire et al. 1980; Kocsis et al. 1993; Honig et al. 1999; Lund et al. 1982; Kessing 1998), but fortunately the insult does not seem to be cumulative (Engelsmann et al. 1988). More specifically, lithium impairs both mental and motor speed, short-term memory and verbal or associative fluency, but the deficit is reversible when lithium is withdrawn and re-establishes when lithium is re-administered (Goldberg 2008; Shaw et al. 1987; Kocsis et al. 1993). Lithium also causes a deficit in the long-term recall (retrieval) without having an effect on attention or encoding (Shaw et al. 1987; Squire et al. 1980; Reus et al. 1979; Karniol et al. 1978; Kropf and Muller-Oerlinghausen 1979). This deficit might especially concern verbal memory (Bora et al. 2007; Senturk et al. 2007). The overall effect size related to the negative impact of lithium treatment on neurocognition is small (Arts et al. 2008), but could be significant concerning specific domains (Wingo et al. 2009). Precise guidelines concerning lithium treatment and its optimal therapeutic levels are available (Malhi et al. 2011).

The recommended valproate therapeutic serum concentration is 50–150 mg/ml. It needs caution when used in women of childbearing age, due to the high frequency of unplanned pregnancies in bipolar females and the relatively high teratogenicity of valproate. Other potential acute side effects are weight gain and hair loss. It is unclear whether it induces polycystic ovarian syndrome.

The typical dosage of carbamazepine in the treatment of acute mania is 600–1,800 mg/day (serum concentration 4–12 mg/ml). However, after several weeks under carbamazepine, an induction of hepatic enzymes (CYP 3A4) occurs. Consequently the drug levels drop and may require additional upward dose titration (Bertilsson and Tomson 1986). The dosage-related adverse effects include double or blurred vision, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, cognitive impairment, haematological effects and Stevens–Johnson syndrome and its related dermatological effects (Tohen et al. 1991, 1995; Blackburn et al. 1998).

The most significant drawback of lamotrigine treatment is the need to initiate it slowly with a rate of 25 mg at 2-week intervals in order to avoid a moderately high incidence of dangerous rash (Seo et al. 2010).

Carbamazepine decreases lamotrigine concentrations by approximately 50 %, and during combination therapy, lamotrigine can be started with higher dosages and faster titration. It exerts similar effects on other agents as well, e.g. risperidone (Ono et al. 2002).

It is also important to note the adverse effects of topiramate because although it is not used in the treatment of BD per se, it is often administered in BD patients in order to lose weight or to treat a comorbid substance abuse disorder. It is reported that topiramate impairs attention, verbal memory, psychomotor slowing, and word finding even at very low dosages (25–50 mg/day). This impairment is reversible after discontinuation of the drug (Goldberg 2008; Salinsky et al. 2005).

The adverse effects of FGAs and especially of haloperidol include extrapyramidal signs and symptoms (EPS), tardive dyskinesia and hyperprolactinaemia, while the most frequent side effects of chlorpromazine are EPS, tardive dyskinesia, postural hypotension and hepatotoxicity. On the other hand, the most significant problem with some of the SGAs is weight gain, hyperlipidaemia and diabetes mellitus in a significant percentage of the patients. The treatment of these somatic conditions is difficult, and the methods proposed have produced rather unsatisfactory results so far. Hyperprolactinaemia and EPS are the most frequent adverse effects with amisulpride. Akathisia and EPS are the adverse effects most often reported with aripiprazole.

Concerning olanzapine, the most frequent adverse effects include dry mouth, weight gain, increased appetite, diabetes mellitus and metabolic syndrome and somnolence. The main adverse effects of quetiapine are persistent sedation and weight gain, however, to a lower extent than olanzapine. Maybe the XR formulation of quetiapine induces less sedation in comparison to the IR formulation (Riesenberg et al. 2012). The main side effects of risperidone are dose-related EPS, weight gain, sedation and hyperprolactinaemia. Somnolence, akathisia and EPS, as well as a potential QTc prolongation, are the main adverse effects of ziprasidone treatment; however, ziprasidone is not associated with the metabolic syndrome (Kemp et al. 2012b).

Reports on antipsychotics concerning their adverse effect on neurocognition are rare and conflicting (Holmes et al. 2008; Pan et al. 2011; Goldberg and Chengappa 2009). There are data suggesting that the executive function deficit was correlated with years of exposure to antipsychotic drugs (Zubieta et al. 2001). This latter finding could reflect the toxic effect of chronic psychosis, the toxic effect of long-term medication or both. In general, neuroleptics have been associated with sustained attention and visuomotor speed deficits (King 1994). Current antipsychotic treatment in BD patients is reported to relate to worse performance across all executive function tests as well as in semantic fluency, verbal learning and recognition memory, even when clinical features were controlled for (Frangou et al. 2005; Jamrozinski et al. 2009; Altshuler et al. 2004).

16.2.8 Switching to the Opposite Pole

There were several reports in the 1970s suggesting that the use of antidepressants might induce mania, mixed episodes and rapid cycling. On the other hand, there is a wide belief among clinicians that antipsychotics induce depression. Often these two suggestions are not limited to BD but are considered to be true for all mental disorders. Overall, it is widely accepted among psychiatrists that both antidepressants and FGAs can induce the opposite pole, a chronic, dysphoric, mixed or irritable state in BD patients, and may accelerate episode frequency and/or may cause other forms of course destabilization in patients with BD. However, hard data are rare, and the bulk of evidence comes from chart reviews and retrospective and open studies.

The earlier studies utilized the medical records of patients in a retrospective way and suggested that without the concomitant use of an antimanic agent, the switch rate to mania or hypomania is around 25 % (Bottlender et al. 2001). Additionally they suggested that the concomitant use of an antimanic agent reduces the switch rate to 14 % but does not eliminate the risk (Post et al. 2001, 2006). It seems also that the switch rate depends on lithium levels (5.9 % for high and 10.5 % for low lithium levels) (Nemeroff et al. 2001). The review of the medical records of 158 depressed BD-I patients suggested that pharmacological intervention and the number of mixed depressive symptoms at admission acted as risk factors for the development of manic-like symptomatology (Bottlender et al. 2004).

The analysis of the results of the STEP-BD patients is of particular interest. The results from the first 500 patients reported that from the 338 subjects with prior antidepressant treatment and complete data on switch event outcomes, 44 % reported at least 1 switching. Shorter duration of illness and history of multiple antidepressant trials seemed to act as risk factors. Also switch was less common during treatment with electroconvulsive therapy or monoamine oxidase inhibitors than other antidepressants (Truman et al. 2007). The results from the first 1,500 patients suggested a 10 times higher risk for the presence of dysphoria, irritability and middle insomnia for those patients with current antidepressant treatment although this could be predicted also by past antidepressant-related manic switch and gender (El-Mallakh et al. 2008).

The data from double-blind RCTs concerning the switch rates of paroxetine and bupropion suggest that they are similar to placebo (Sachs et al. 2007). A problem is that since paroxetine is not efficacious in the treatment of acute bipolar depression (McElroy et al. 2010c), no real conclusions can be made. The data are also negative for fluoxetine even as monotherapy in BD-II patients (Amsterdam et al. 2004) and for citalopram whose rates are similar to those of lamotrigine when added on a mood stabilizer (Schaffer et al. 2006).

However there are some data suggesting that venlafaxine might have higher rates of switching in comparison to the other antidepressants or placebo. The results from a 10-week RCT, on 174 patients which were randomly treated with a flexible dose of bupropion, sertraline and venlafaxine or placebo as adjuncts to mood stabilizers, suggested that while the three antidepressants were comparable in terms of efficacy, there was a significantly increased risk of switches into hypomania or mania in those patients treated with venlafaxine in comparison to bupropion or sertraline (Post et al. 2006). The comparison of venlafaxine with bupropion after 1 year found higher rates of switch into hypomania and mania in the venlafaxine group (21.8 % vs. 14.9 %) (Leverich et al. 2006). A small study which compared 15 BD-II depressed women with 17 women with unipolar depression which were randomized to receive once vs. twice daily venlafaxine monotherapy up to 225 mg for 6 weeks reported similar efficacy for venlafaxine in the two diagnostic groups without any episodes of drug-induced hypomania or rapid cycling (Amsterdam and Garcia-Espana 2000). A single-blind 6-week comparison of paroxetine vs. venlafaxine in 55 bipolar depressed patients which were already receiving mood stabilizers reported no significant differences in either efficacy or safety between the two treatment groups; however, although the dropout rate was similar (43 % vs. 50 %), more patients under paroxetine dropped out because of lack of efficacy (7 % vs. 0 %), while more under venlafaxine dropped out because of switching to mania (3 % vs. 13 %) (Vieta et al. 2002). Two more recent publications from the same research group reported conflicting results concerning venlafaxine (Altshuler et al. 2006, 2009). The interpretation of the data concerning venlafaxine is difficult, but one of the available interpretations could be that venlafaxine is efficacious in the treatment of bipolar depression but at the same time puts patients at a higher risk to switch to mania or hypomania. This switch causes dropouts and could mask the therapeutic effect.

Similarly, there are data suggesting that treatment with imipramine increases the risk for an affective switch. A small 6-week study on BD patients suffering from 'anergic depression' compared the efficacy of tranylcypromine (30–60 mg/day; $N=28$) with that of imipramine (150–300 mg/day; $N=28$), and the results suggested that tranylcypromine produced statistically significant superior outcome in terms of greater symptomatic improvement, while the proportion of patients which switched to mania/hypomania was numerically higher in the imipramine group (12 % vs. 24 %). BD-I patients had a significantly greater risk of treatment-emergent mood swings (38 % vs. 13 %; $p=0.03$) (Himmelhoch et al. 1991). Another 8-week international multicentre study in 156 bipolar depressed patients randomized them to moclobemide (450–750 mg/day; $N=81$) or imipramine (150–250 mg/day; $N=75$). There were no statistically significant differences between the two groups on any

efficacy measures or on the dropout rate for any reason; however, more patients under imipramine switched to mania (3.7 % vs. 11 %) (Silverstone 2001). Finally, a multicentre 10-week study in 117 BD depressed outpatients compared paroxetine (20–50 mg/day; $N=35$) vs. imipramine (50–300 mg/day; $N=39$) vs. placebo ($N=43$) as add-on to lithium and reported that the three groups were comparable in terms of efficacy; however, in comparison to imipramine, paroxetine resulted in a lower incidence of the emergence of manic symptoms (Nemeroff et al. 2001).

It is important to mention that switching to mania or hypomania has been reported during treatment with antidepressants of comorbid OCD (White et al. 1986; Steiner 1991; Vieta and Bernardo 1992; Rihmer et al. 1996; Perugi et al. 2002) or panic disorder (Pecknold and Fleury 1986; Sholomskas 1990).

There are a number of reviews which suggest a possible connection between switching and antidepressant treatment; however, they also stress that all available studies suffer from various forms of bias. The switch rate has been calculated to be as high as 18.2 % in the short term and 35.6 % during the continuation phase; however, it has also been pointed out that antidepressant discontinuation is associated with a substantially increased risk of depression relapse over the subsequent year with no reduced risk of switching into mania (Post et al. 2003). The risk is higher in BD-I patients in comparison to BD-II (14.2 % vs. 7.1 % in acute trials and 23.4 % vs. 13.9 % in maintenance studies). The rates of switching in unipolar patients are lower than those in bipolar (1.5 % in acute trials and 6.0 % in maintenance studies) (Bond et al. 2008). Another review suggested that all classes of antidepressants have been reported to relate to affective switches in a subgroup of about 20–40 % of BD patients. The patients at the highest risk seem to be those whose initial illness begun in adolescence or young adulthood (Goldberg and Truman 2003). Furthermore, it is reported that when combined with a mood stabilizer, antidepressants given for acute bipolar depression do not induce a switch into hypomania or mania (Licht et al. 2008; Harel and Levkovitz 2008). The most recent systematic review of 73 reports (109 trials, 114 521 adult patients), 35 of which were suitable for meta-analysis, suggested that the overall risk of mania with vs. without antidepressants averaged 12.5 % vs. 7.5 %, with antidepressant-associated mania being more frequent in bipolar than unipolar patients. TCAs were riskier than SSRIs, while data for other types of ADs were inconclusive. Mood stabilizers had minor effects probably confounded by their preferential use in mania-prone patients (Tondo et al. 2010). A genetic study of BD-I ($N=103$) and BD-II ($N=66$) patients during antidepressant therapy, who manifested an affective switch that occurred within a period of 3 weeks in comparison to 247 patients which never showed switches concerning the functional polymorphism in the upstream regulatory region of the serotonin transporter (SERTPR), tryptophan hydroxylase (TPH), G-protein beta 3 subunit (Gbeta3), monoamine oxidase A (MAO-A), catechol-O-methyltransferase (COMT), serotonin receptor 2A (5-HT2A), dopamine receptor D2 (DRD2) and dopamine receptor D4 (DRD4) gene variants, produced no significant results (Serretti et al. 2004).

FGAs are also considered to induce the opposite pole and cause dysphoria and depression. Although one study in acutely manic patients suggested that

haloperidol-treated patients relapsed earlier than olanzapine-treated patients into a depressive episode, this could simply mean that haloperidol is less effective than olanzapine in the prevention of depressive episodes (Tohen et al. 2003a). On the contrary, one trial which compared continuation treatment of perphenazine vs. discontinuation (placebo) as adjunct on lithium, carbamazepine or valproate for 6 months reported that those patients randomly assigned to continue perphenazine treatment, relative to those who discontinued it, were more likely to have a shorter time to depressive relapse, discontinue the study and have increased rates of dysphoria, depressive symptoms and extrapyramidal symptoms (Zarate and Tohen 2004).

On the contrary, in most studies SGAs do not appear to switch patients into depression, while some authors suggest they possess a mild protective property against switching. Both SGAs and the OFC seem to be efficacious without posing the patients at an increased risk for an affective switch (Tohen et al. 2003c; Amsterdam and Shults 2005a; Keck et al. 2005; Benazzi et al. 2009; Calabrese et al. 2005a; Thase et al. 2006). A recent meta-analysis reported that treating acute mania with SGAs is associated with 42 % less risk of switch to depression than with haloperidol. Nevertheless, caution should be taken when considering this a class effect, as only olanzapine, quetiapine and ziprasidone may show a better profile (Goikolea et al. 2013b).

Overall there are no data to suggest a generalized and class effect for antidepressants or FGAs concerning the induction of an affective switch. There are negative data concerning all SSRIs and SGAs studied and some positive data only concerning venlafaxine, imipramine and perphenazine. Some authors believe that at least the switch risk and perhaps also the risk for rapid cycling and new-onset suicidality have been over-interpreted (Grunze 2008).

Conclusively, the issue of switching is still open and further research is needed. No solid conclusions can be made so far. A summary of the data concerning the switch risk is shown in Table 16.9.

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