Eur Arch Psychiatry Clin Neurosci (2003) 253 : 115–119 DOI 10.1007/s00406-003-0427-4

SPECIAL ISSUE

Heinz Grunze

Lithium in the acute treatment of bipolar disorders – a stocktaking

Accepted: 7 May 2003

Abstract Before the rise of atypical antipsychotics, lithium used to be the most frequently investigated substance in the acute treatment of bipolar disorders, although studies are not always of the highest methodological standard. Due to the doubt about a sufficient efficacy of lithium expressed in recent years from various sides, and the simultaneous availability of newer treatment alternatives, this paper attempts to make a critical stocktaking of our knowledge about lithium in the acute treatment of bipolar disorders. Aspects concerning the changed disorder concept through the broadening of the bipolar spectrum, together with the available results from controlled and open studies with lithium, are presented and appraised. This shows that lithium should still be seen as an essential, but not the only corner stone in the differentiated treatment of bipolar patients. Provided that it is taken reliably and well-tolerated, lithium represents a first choice treatment, particularly for a classical course of manic-depressive illness (Bipolar I disorder), especially for mild to moderate manic syndromes. However, as antidepressive treatment, lithium should rather not be applied as a monotherapy, particularly in severe bipolar depression, since with the new generation of antidepressants and anticonvulsants well-tolerated and very effective alternatives are available. In combination treatment, lithium should be applied particularly when it has already shown good prophylactic efficacy and/or in patients for whom a high suicide risk must be presumed.

Key words bipolar disorder · depression · lithium · mania

Dr. H. Grunze (✉)
Psychiatrische Klinik der LMU
Nussbaumstr. 7
80336 München
Tel.: +49-89/5160-5335
Fax: +49-89/5160-5330
E-Mail: grunze@psy.med.uni-muenchen.de

Introduction

Over 50 years ago, Cade first described the antimanic efficacy of lithium. Even though his studies must rather be described as not complying to modern methodological standpoints, it was still the first time that psychiatrists were given an effective drug treatment for mania. Extensive further studies, especially by Mogen Schou, followed in the subsequent decades, so that by the beginning of the 1970s lithium treatment of bipolar patients had become established in antimanic acute therapy, and particularly in relapse prophylaxis (Goodwin and Zis 1979; Schou 1997; Bowden 1998). Even before the discussion about the switch risk of antidepressants was initiated, the acute antidepressive efficacy of lithium continued to be followed in smaller studies (Overview in Adli et al. 1998). However, due to the lack of commercial interest from pharmaceutical companies, large controlled studies were never performed, which are considered conclusive for acute antidepressive efficacy according to the methodological standards expected today (EMEA guidelines). As regards antimanic treatment, in the meantime lithium has also satisfactorily delivered placebo-controlled proof of efficacy, so to speak via the back door, as a comparator substance for trials with new potential antimanic compounds (e. g., versus valproate as a test substance and placebo (Bowden et al. 1994)).

Besides the question of the efficacy and side effect profile, the most important aspect of lithium treatment is the question which predictors make an individual patient suitable for lithium treatment, i. e. make treatment success with simultaneous good tolerability at least probable. Most studies with lithium were conducted when the diagnostic criteria for a manic-depressive disorder were still very tight. They corresponded to today's bipolar I disorder according to ICD 10 with omission of so-called atypical symptoms (e. g., psychotic features, mixed states). Accordingly, most studies with lithium also just included such patients as a homogenous group. The newer Phase III studies also include only bipolar I

patients, in order to guarantee comparability of the samples, even if atypical symptoms, as just mentioned, are no longer a strict exclusion criterion. Besides this selection of patients, which is very restrictive according to today's understanding of bipolar disorder as a spectrum of illnesses, a critical evaluation of the studies also has to consider that such a patient sample is also special in other respects (Bowden et al. 1995; Licht et al. 1997). Study patients generally also experience particular observation by close-meshed and standardised evaluation appointments, which in turn is reflected in good drug compliance, which should definitely be rated as higher than under normal conditions. Studies prove "efficacy", but not "effectiveness". A critical recommendation for clinical practice must therefore bear in mind what happens with non-compliant patients. Omission or sudden discontinuation of a drug can also have negative consequences for the course of the disorder. In this regard, for lithium there really are some hints for an increase of severity of the illness course with sudden discontinuation (Goodwin,1994).

Study situation

Treatment of acute mania

So far, a total of 29 published or presented studies have evaluated the acute antimanic efficacy of lithium. Selected studies are shown in Table 1. Lithium therefore has clearly the largest pool of studies with regard to the number that have been performed. Four early studies, starting with Shou's evaluation from 1954 (Schou et al. 1954), tested lithium versus placebo. However, today only the American multi-centre study published in 1994 (Bowden et al. 1994) can be considered as corresponding to the current methodological standards for a drug approval study. It was performed with 3 arms comparing an active substance (valproate), lithium and placebo, in a large enough number of patients to reach statistical significance with a low probability of error, and is not based on a patient sample that is pre-selected with respect to a previous response to lithium. Furthermore, the use of rescue medication was controlled and limited. All of these are aspects that were not considered in earlier studies, or at least not all of them were considered. To avoid a misunderstanding, this does not represent negligence on the part of the investigators, but only reflects the change in the requirements of the registration authorities. However, also for the study by Bowden et al. it must be critically noted that only a fraction of the potentially suitable patients were randomised, and that only a third of all patients reached the study endpoint. Obviously selection processes were also involved here, which render more difficult the transferral of the results to clinical practice.

Recently, lithium was also used in four studies as a standard comparator in testing a new anticonvulsant against placebo in acute mania. In all studies, lithium significantly outperformed placebo. However, as these trials failed for the test substance, these studies may never get published.

In other studies, the antimanic efficacy of lithium was mainly tested versus various antipsychotics (a total of 11 studies versus chlorpromazine and/or haloperidol, one versus olanzapine (Berk et al. 1999) and risperidone (Segal et al. 1998) and versus carbamazepine (5 studies)). The response rates given for lithium in randomised studies (whereby different treatment duration and responder criteria were applied from study to study) range from 32% (Small et al. 1991) to 94% (Freeman et al. 1992). One of the explanations for this wide range is the variance of the severity of the manic syndromes in the various studies. The average baseline value in Bowden's study of 27 points on the Mania Rating Scale of the SADS (Spitzer et al. 1975) corresponds clinically to a moderately severe to severe mania and showed a lithium responder rate of 49%. However, other studies with higher success rates were mostly performed in outpatients (e. g. (Freeman et al. 1992; Berk et al. 1999)).

To summarise, the efficacy of lithium as reflected by this bulk of studies appears to be at least equal to that of carbamazepine, valproate, clonazepam and several antipsychotics. This is also confirmed by meta-analysis of the studies with lithium, valproate and/or carbamazepine (Emilien et al. 1996). Particularly the study by Bowden (Bowden et al. 1994) was followed by several retrospective subgroup analyses, which suggested that

Table 1 Lithium in the acute treatment of mania (selected studies)

Authors	Duration of study	Design	Efficacy
Johnson et al. (1968)	3–4 weeks	Lithium (n = 18) Chlorpromazine (n = 11)	LI: 78% CPZ: 36%
Shopsin et al. (1975)	21 days	Lithium (n = 10) Haloperidol (n = 10) Chlorpromazine (n = 10)	LI = HLD LI ≥ CPZ
Small et al. (1991)	8 weeks	Lithium (n = 24) Carbamazepine (n = 24)	LI = CBZ
Bowden et al. (1994)	21 days	Lithium (n = 35) Valproate (n = 68) Placebo (n = 73)	LI: 49%, VPA: 48%, PLC: 25% LI > PLC; VPA > PLC LI = VPA
Walton et al. (1996)	28 days	Lithium (n = 19) Verapamil (n = 21)	LI > VP

lithium shows a somewhat better response than valproate in classical euphoric mania, whereas valproate rather shows advantages over lithium in the so-called mixed states (Swann et al. 1997). In very severe and psychotic mania, however, typical antipsychotics may be more advantageous than lithium (Johnstone et al. 1988).

As regards the most frequent side effects, in the study by Bowden (Bowden et al. 1994), compared to placebo or valproate lithium showed vomiting, fever and involuntary twitches as side effects significantly more frequently. The frequency of study discontinuation due to lithium side effects was 11 % (to compare: valproate 6 %, placebo 3 %). Side effects that can become relevant for continuation therapy and maintenance (see relevant section), such as weight gain or cognitive deficits, are of less importance during the short treatment periods for acute mania.

The slightly delayed commencement of effect is seen as a disadvantage of lithium compared to the other antimanic substances; it is caused by the slower dosage titration for lithium, e. g. in comparison to valproate or olanzapine. In clinical practice this may result in a higher use of typical antipsychotics to bridge this period, particularly in severe mania. However, these should be avoided when possible, due to their known side effects of early and tardive dyskinesia. On the other hand, successful and fast dosage increase of lithium was described in small open studies by Thau (Thau et al. 1991) and Keck (Keck et al. 2001), but this appears less pragmatic in practice due to the necessity for closely-meshed controls of blood levels to minimise the risk of intoxication.

The question whether this delayed onset of action of lithium may also have an overall impact on the treatment of mania concerning the duration of hospitalisation is answered controversially. An analysis of the duration of hospitalisation for acute mania by Keck, comparing lithium and valproate monotherapy and lithium/carbamazepine combination treatment was clearly in favour of valproate monotherapy and lithium/carbamazepine combination treatment (Keck et al. 1996). However, a recent chart analysis found no statistically significant difference between lithium and valproate as far as the length of stay in hospital is concerned (11.5 ± 6.9 for patients on valproate and 10.3 ± 5.2 days for patients on lithium, respectively) (Moncrieff 1997).

In summary, for the acute treatment of mania it can be stated that the efficacy of lithium has been demonstrated for the treatment of acute mania in bipolar I disorders. However, owing to the higher rate of side effects and the delayed onset of action, e. g. in comparison to valproate, lithium should not be the only drug of first choice when acute antimanic treatment is needed. This changes when a patient was previously stabilised on lithium, where possibly only an increase of the dose is required to achieve sufficient antimanic efficacy, or, with a view to the long-term course of the disorder, lithium should be considered anyway for relapse prevention or reduction of the suicide risk (Thies-Flechtner et al. 1996).

Treatment of bipolar depression

A recently published overview (Adli et al. 1998) summarises the available positive studies suggesting acute efficacy of lithium in bipolar depression (see Table 2). While for mania there is at least one methodologically acceptable study available that demonstrates, according to current registration standards, the efficacy of lithium,

Table 2 Randomized, double-blind monotherapy studies of lithium in depression with positive outcome (adapted from Adli et al. 1998)

Authors	No of patients (N) and gender (F/M)	No of patients with Li/comparator	Comparator	Duration	Dosages (blood levels)	Result
Mendels et al. (1972)	13 bipolar, 11 unipolar; 14F/10M	12/12	desipramine (25 mg/d)	3 weeks	TCA or Li (250 mg/d starting dose), optimization of Li serum level at day 4.7.14	Li = desipramine
Watanabe et al. (1975)	Mixed diagnoses, with 5 patients with "circular type depression", 18F/27M	26/19	imipramine (75–150 mg/d)	3–5 weeks	TCA or Li (450–900 mg/d), max. Li-serum level 1.2 mEq/l	Li = imipramine
Worrall et al. (1979)	17 unipolar, 4 with uncertain diagnosis, 29F	14/15	imipramine (starting dose 25 mg/d)	3 weeks	TCA or Li, Li-serum level 0.8–1.2 mEq/l	Li > imipramine
Khan (1981)	No information on diagnosis, 19F/11M	12/13	amitriptyline (75 mg/d)	3 weeks	TCA or Li (800 mg/d)	Li = amitriptyline
Arieli & Lepkifker (1981)	11 bipolar, 22 unipolar, 21 F/12 M	12/10/11 placebo	clomipramine, placebo	3 weeks	TCA or Li (1500–2500 mg/d)	Li = clomipramine > placebo
Kahn et al. (1987)	3 bipolar, 27 unipolar, 1 schizoaffective; 24 F/7 M	16/15	placebo	6 weeks	PLC or Li (800 mg/d), adaption of Li-serum level (0.5–1.0 mEq/l)	Li > PLC
Linder et al. (1999)	3 bipolar, 19 unipolar; 14F/8M	10/12	clomipramine (100 mg/d)	4 weeks	TCA or Li (32.4 mmol/d), every 4th day adaption of Li serum level (0.7–1.1 mEq/l)	Li = clomipramine

there is unfortunately no such study for bipolar depression. Those studies depicted in Table 2 demonstrated to a greater or lesser degree antidepressive effects of lithium (probably slightly better in bipolar than in unipolar depression (Goodwin et al. 1972)) but in the end they are all underpowered to allow any firm conclusion. The meta-analytical approach (Souza and Goodwin, 1991) may further reinforce this impression of antidepressive efficacy, but in the end is also no proof. Of the various positive studies, the investigations by Mendels (Mendels et al. 1972) and Arieli and Lepkifker (Arieli and Lepkifker 1981) appear to be the most convincing, since they at least treat a somewhat larger sample of bipolar patients (n = 13 and 11, respectively). However, the largest double-blind monotherapy study comparing lithium to imipramine in 29 bipolar depressed patients points towards superiority of imipramine (Fieve et al. 1968). As an additional aspect, similar to the case in the treatment of mania, this study also underlined the problem of a delayed commencement of action of lithium caused by the dose titration phase. Even though a long-term antisuicidal effect of lithium can be assumed (Thies-Flechtner et al. 1996), this of course represents a problem in the treatment of severely depressive and acutely suicidal patients. Considering long-term efficacy, the capability of lithium to prevent new depressive episodes may also be less pronounced compared to the prevention of mania (Burgess et al. 2001; Geddes et al. 2002).

With respect to symptom and frequency, the side effects described in the studies do not differ, or at least not significantly, from those described for the treatment of mania.

To summarise, based on the efficacy of lithium in the treatment of depression demonstrated in some small, double-blind comparator studies, lithium can be considered as a treatment possibility for bipolar depression in cases of mild to moderately severe depression, when a certain latency until the start of action appears justifiable. If necessary, this period can be bridged in the short-term by administration of a benzodiazepine, e. g. in cases of agitation or sleeplessness. This treatment option should also be chosen when the patient is a classical bipolar I and was previously stabilised on lithium (then dose increase) or if he is a candidate for lithium in the long-term. Contrary to older American recommendations, some of which, even for the severest depression, recommend monotherapy with a mood stabiliser or combination treatment with several mood stabilisers instead of administration of an antidepressant (Sachs, 1996) in cases of severe depression the primary combination treatment should always be with an antidepressant (Möller et al. 2001; Grunze et al. 2002a, b). Due to the so-called switch risk of tricyclic antidepressants (Peet 1994), serotonin re-uptake inhibitors or reversible MAO inhibitors should be used preferentially (Boerlin et al. 1998; Bottlender et al. 1998; Grunze and Möller 2002). In this combination, besides its own antidepressive effect, lithium can simultaneously offer high, although not 100 % protection against such a switch. In case of intolerability to lithium, or in the presence of atypical symptoms or illness courses that rather contraindicate relapse prophylaxis with lithium, various antiepileptics can be used (carbamazepine, valproate and, as of late, also lamotrigine). To date too little is known about the relapse prophylactic value of atypical antipsychotics to allow their uncritical recommendation. However, they should definitely be considered as an additional medication in the presence of delusional symptoms as part of a depression, or of sleep disorders.

Discussion

Not so much due to its high efficacy in acute treatment, but particularly because of its relapse prophylactic and presumed antisuicidal properties, lithium continues to represent an important corner stone in the treatment of bipolar patients. As long as the newer substances have not demonstrated the same efficacy, also backed up by the accumulated wealth of experience from many years, in these two areas (relapse prophylaxis and antisuicidal efficacy) lithium remains a primary choice. Administration as an acute treatment is surely based on the long-term aspect of the treatment. Lithium should therefore be the treatment of first choice either in patients who were previously stabilised on lithium and had been treated well with it in relapse prophylaxis for a long time, or in those predestined for long-term lithium prophylaxis based on the characteristics of their disease (classical bipolar I disorder) and on reliable compliance with medication use. However, in most cases, but above all for severe acute symptoms, concomitant therapy is unavoidable, e. g. antipsychotics in mania or antidepressants in depression. Particularly in the case of depression, monotherapy with a mood stabiliser, whether lithium or an antiepileptic, should currently still be avoided since as yet no study that could not be criticised with respect to its methodology could demonstrate equal efficacy of a mood stabiliser compared to a standard antidepressant (Möller and Grunze 2000). It is very difficult to give clear treatment recommendations for patients with atypical illness courses (psychotic manias, mixed states, rapid cycling) or bipolar II disorders and schizoaffective disorders. Although the evaluations to date do indicate a tendency towards superiority of antiepileptics, particularly valproate, or of atypical antipsychotics in acute treatment, one must say that overall the number and quality of studies has improved only recently. So far, either only uncontrolled studies were available, or the conclusions have arisen from retrospective analyses of controlled studies and small numbers of patients. With the recent phase III trials of atypical antipsychotics, especially olanzapine, we now have also controlled data supporting comparable efficacy in atypical manifestations as mixed states, rapid cycling and psychotic mania (Bhana and Perry 2001), and even in patients with marked depressive features (Dube et al.

2002). However, it is definitely to be advised against discontinuing lithium just based on these first indications, for example in a patient with a schizoaffective or bipolar II disorder who was previously successfully treated with lithium, and to change to a different mood stabiliser. The administration of a second mood stabiliser or atypical antipsychotic may well be indicated in acute treatment, but it depends on the previous illness course whether the long-term continuation of a then two-track episode prophylaxis is indicated.

References

1. Adli M, Bschor T, Canata B, Döpfmer S, Bauer M (1998) Lithium in der Behandlung der akuten Depression. Fortschr Neurol Psychiatr 66:435–441
2. Arieli A, Lepkifker E (1981) The antidepressant effect of lithium. Curr Dev Psychopharmacol 6:165–190
3. Berk M, Ichim L, Brook S (1999) Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. Int Clin Psychopharmacol 14:339–343
4. Bhana N, Perry CM (2001) Olanzapine: a review of its use in the treatment of bipolar I disorder. CNS Drugs 15:871–904
5. Boerlin HL, Gitlin MJ, Zoellner LA, Hammen CL (1998) Bipolar depression and antidepressant-induced mania: a naturalistic study. J Clin Psychiatry 59:374–379
6. Bottlender R, Rudolf D, Strauß A, Möller H-J (1998) Antidepressant-associated maniform states in acute treatment of patients with bipolar I depression. Eur Arch Psychiatry Clin Neurosci 248:296–300
7. Bowden CL (1998) Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. J Clin Psychiatry 59 (Suppl 6):13–19
8. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsaver SC, Davis JM, Rush AJ, Small JG, Garza-Trevino ES, Risch SC, Goodnick PJ, Morris DD (1994) Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 271:918–924
9. Bowden CL, Calabrese JR, Wallin BA, Swann AC, McElroy SL, Risch SC, Hirschfeld RM (1995) Who enters therapeutic trials? Psychopharmacol Bull 31:103–109
10. Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G (2001) Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev CD003013
11. Dube S, Andersen S, Clemow D, Sanger T, Tohen M, Tollefson G (2002) Olanzapine-fluoxetine combination for treatment of psychotic depression. Eur Psychiatry 17 (Suppl 1):130
12. Emilien G, Maloteaux JM, Seghers A, Charles G (1996) Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. Eur Neuropsychopharmacol 6:245–252
13. Fieve RR, Platman SR, Plutchik RR (1968) The use of lithium in affective disorders. I. Acute endogenous depression. Am J Psychiatry 125:487–491
14. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC (1992) A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 149:108–111
15. Geddes J, Goodwin G, Rendell J, Hainsworth J, Van der GE, Young H (2002) New trial should clarify lithium use in bipolar disorder. BMJ 325:441
16. Goodwin FK, Murphy DL, Dunner DL, Bunney WE (1972) Lithium response in unipolar versus bipolar depression. Am J Psychiatry 129:44–47
17. Goodwin FK, Zis AP (1979) Lithium in the treatment of mania: comparisons with neuroleptics. Arch Gen Psychiatry 36:840–844
18. Goodwin GM (1994) Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. Br J Psychiatry 164:149–152
19. Grunze H, Kasper S, Goodwin G, Bowden CL, Baldwin D, Licht RW, Vieta E, Möller H-J, WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2002a) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders. Part I: Treatment of Bipolar Depression. World J Biol Psychiatry 3:115–124
20. Grunze H, Möller H-J (2002) The place of antidepressants in the acute treatment of bipolar disorder. Clinical Approaches in Bipolar Disorders 1:40–46
21. Grunze H, Walden J, Dittmann S, Berger M, Bergmann A, Bräunig P, Dose M, Emrich HM, Gastpar M, Greil W, Möller H-J, Uebelhack R (2002b) Psychopharmakotherapie Bipolarer Affektiver Erkrankungen. Nervenarzt 73:4–17
22. Johnstone EC, Crow TJ, Frith CD, Owens DG (1988) The Northwick Park "functional" psychosis study: diagnosis and treatment response. Lancet 2:119–125
23. Keck PE, McElroy SL, Bennett JA (1996) Health-economic implications of the onset of action of antimanic agents. J Clin Psychiatry 57 (Suppl 13):13–18
24. Keck PE, Strakowski SM, Hawkins JM, Dunayevich E, Tugrul KC, Bennett JA, McElroy SL (2001) A pilot study of rapid lithium administration in the treatment of acute mania. Bipolar Disord 3:68–72
25. Licht RW, Gouliaev G, Vestergaard P, Frydenberg M (1997) Generalisability of results from randomised drug trials. A trial on antimanic treatment. Br J Psychiatry 170:264–267
26. Mendels J, Secunda SK, Dyson WL (1972) A controlled study of the antidepressant effects of lithium carbonate. Arch Gen Psychiatry 26:154–157
27. Moncrieff J (1997) Lithium: evidence reconsidered. Br J Psychiatry 171:113–119
28. Möller H-J, Grunze H (2000) Have some guidelines for the treatment of acute bipolar depression gone too far in the restriction of antidepressants? Eur Arch Psychiatry Clin Neurosci 250:57–68
29. Möller HJ, Bottlender R, Grunze H, Strauss A, Wittmann J (2001) Are antidepressants less effective in the acute treatment of bipolar I compared to unipolar depression? J Affect Disord 67:141–146
30. Peet M (1994) Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 164:549–550
31. Sachs GS (1996) Treatment-resistant bipolar depression. Psychiatr Clin North Am 19:215–236
32. Schou M (1997) Lithium-Behandlung der manisch-depressiven Krankheit. Thieme, Stuttgart
33. Schou M, Juel-Nielsen N, Strömgren E, Voldby H (1954) The treatment of manic psychoses by the administration of lithium salts. J Neurol Neurosurg Psychiatry 17:250–260
34. Segal J, Berk M, Brook S (1998) Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 21:176–180
35. Small JG, Klapper MH, Milstein V, Kellams JJ, Miller MJ, Marhenke JD, Small IF (1991) Carbamazepine compared with lithium in the treatment of mania. Arch Gen Psychiatry 48:915–921
36. Souza FG, Goodwin GM (1991) Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry 158:666–675
37. Spitzer RL, Endicott J, Robbins E (1975) Research Diagnostic criteria (RDC) for a selected group of functional disorders. New York Psychiatric Institute, New York
38. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, Dilsaver SC, Davis JM (1997) Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 54:37–42
39. Thau K, Meszaros K, Simhandl C (1991) Three cases of severe mania successfully treated with high-dosage lithium-carbonate. Pharmacopsychiatry 24:85–88
40. Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W (1996) Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. Pharmacopsychiatry 29:103–107