Combination therapy for manic phases: a critical review of a common practice.

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ABSTRACT

All relevant guideline recommend monotherapy as the initial treatment for manic phases of bipolar disorder (BD), with combination therapy reserved for severe cases or as a subsequent choice. However, in routine practice, monotherapy is often not sufficiently effective for acute and/or maintenance therapy. As a consequence, most patients are given combination therapies. An extensive search concerning combination treatment for manic episodes was conducted for relevant international randomized controlled studies, treatment guidelines and comprehensive reviews published since 1980. The scientific literature is sufficiently rich to validate the superiority of combination therapy over monotherapy in the manic phase in terms of efficacy and prevention of relapse; its safety profile is acceptable. Side effects are more frequent with combination therapy as a whole than with monotherapy, and discontinuation rates due to adverse events are higher. Continued administration of antipsychotics after a manic phase is controversial: drug classification, the course of the disease and the predominant polarity should all be considered before treatment is continued. Combinations including olanzapine and asenapine and to a lesser extent risperdal are associated with weight gain, those including quetiapine, haldol and asenapine with sedation, and those with aripiprazole akathysia. This review of literature leads us to suggest that combination therapy including an atypical antipsychotic with lithium or valproate may be considered as a first line approach. An appropriate algorithm for making decisions about combination treatment needs to be developed and included in future guidelines.

Keywords: bipolar disorder, mania, combination, adjunction, safety, tolerability, side effects, monotherapy, polytherapy.

INTRODUCTION

Bipolar disorder (BD) type I is a chronic disease characterized by recurrent episodes of mania and depression; these episodes impair in functioning and reduce health-related quality of life. BD requires both acute and maintenance therapy [1]. Several guidelines for the treatment of acute manic states have been published: all of them, consensually, indicate that first-line treatment should be monotherapy [2-6]. They all recommend that the initial treatment for manic episodes should be lithium (Li), valproate (VPA) an atypical antipsychotic (AAP) of other monotherapy. All these expert guidelines agree that any ongoing antidepressant medication should be withdrawn during mania. Combinations are suggested by most guidelines as second-line choice, although in some as first-choice approach for severe mania.

Clinical practice differs from guideline recommendations. Only one in six bipolar patients is discharged on monotherapy medication recommended by the guidelines [7]. Indeed, in routine practice, monotherapy is not sufficient in many cases to obtain a significant reduction in symptoms and/or to effectively prevent relapse, and less than 10% of BD patients receive monotherapy during acute mania episodes [8,9]. Thus, there has been a consistent increase in the use of combination therapy (or polypharmacotherapy) and this is observed worldwide [10]. Wolsfsperger and colleagues showed that polypharmacy is a common phenomenon in treatment of acute mania; they report that the mean number of psychopharmacological agents prescribed per patient is 3.3 ± 1.5, and confirmed that this has increased with time since 1994 [9].

The recent scientific literature also contains various evidence of the better efficacy of combination therapy in manic phases [8]. Our analysis focuses on the efficacy of combination treatment in manic episodes and reviews major pertinent randomized controlled studies.

METHODS

We conducted an extensive search for relevant national and international controlled studies, treatment guidelines and comprehensive reviews published since 1980. The publications were obtained from the Medline electronic database. The literature search was performed using the Mesh heading: "bipolar disorder" OR "manic" OR "mania" AND "combination" OR "adjunction" OR "treatment algorithms". The search was updated until May, 11st, 2012. Only articles written in English were considered as eligible. The figure 1 shows details of the review methods and the search strategy. We included all randomized, double-blind trials comparing one combination (or adjunction) treatment including active antimanic drugs at a therapeutic dose with another active antimanic drug in monotherapy or with placebo as therapy for adults with acute mania. Fifty-nine studies and reviews were included in the qualitative analysis (see figure 1 for details).

- Figure 1 about here -

Strategies of combination treatment for manic phases

Guidelines

The primary goals of treatment of a manic episode are the rapid control of symptoms such as agitation, impulsivity or dangerous behavior, and to allow a return to normal levels of psychosocial functioning [3,4]. Recovery is a multidimensional concept that includes both symptomatic recovery (remission) and functional recovery. In the longitudinal EMBLEM prospective study, 64% of BD type I patients achieved remission and 34% achieved functional recovery [11]. This study showed that patients who presented with acute mania and who took typical antipsychotics or antidepressants for the long-term treatment phase (12 weeks), had lower remission and recovery rates; prescription of APA was associated with a

better remission rate [11]. In addition to the rapidity of symptom control, the issues of tolerability and side-effects of treatment need to be considered.

In guidelines [2-6], favor monotherapy as the first-line approach, for safety and practicability reasons; they recommend making best use of the dose range available for a given medication, since combined treatment is likely to be associated with a cumulated and thus higher frequency and severity of side effects [8]. Combination is recommended as first-line treatment for severe mania in the guidelines of each of the *World Federation of Societies of Biological Psychiatry* WFSBP [2], the *Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders* CANMAT ISBD [4] and the *British Association for Psychopharmacology* BAP [3] and as a second choice for cases of mild and moderate mania after unsuccessful medication in the others guidelines [8]. The American Psychiatric Association guidelines for treating BD recommend combination therapies to treat patients experiencing severe acute manic or mixed episodes and breakthrough manic or mixed episodes during maintenance therapy [12]. However, combination treatment, involving two or more antimanic agents, is routinely used for acute mania episodes in a large majority of BD patients. This divergence between guidelines and clinical practice is probably due to the complexity of the disease, comorbidity and lack of adherence [11].

Clinical trials

Randomized controlled trials (RCT) of combination therapy for the treatment of acute mania are summarized in Table 1. Only randomized, double-blind, controlled studies were included [13-34].

There are very few recent RCT that compare different combination therapies for the treatment of acute manic phases [35]. As combinations are widely used, it would be valuable to compare combination therapies not only to monotherapy but also to others types of combination. This should be the next step of evaluations of the treatment of manic phases.

- Table 1 about here -

One review reports that antipsychotic medication is widely used, being prescribed to between 72% and 92% of patients with mania [36]. The very recent meta-analysis by Cipriani et al. published in the Lancet, compared the efficacy and acceptability of various antimanic drugs in acute mania and found that antipsychotic drugs were significantly more effective than mood stabilizers [37]. In a meta-analysis of randomized, placebo-controlled trials in acute bipolar mania and involving 3,089 subjects, Smith et al. showed that mania scores were significantly more reduced by the following medications than by placebo: carbamazepine, haloperidol, lithium, olanzapine, quetiapine, risperidone, valproate semisodium and aripiprazole [38]. This meta-analysis —which included studies until March 2006—showed that antipsychotics and mood stabilizers are significantly more effective than placebo for the treatment of acute mania, and that the two groups of drug showed similar effect sizes [38]. Also, the study found that haloperidol, olanzapine, risperidone and quetiapine as co-therapy were significantly more effective than monotherapy with a mood stabilizer against mania, but that combinations were less well tolerated than monotherapy [38]. These results confirm the benefits of including an antipsychotic in the treatment if the patient does not fully respond to a mood stabilizer alone.

The superiority of combinations over monotherapy has been demonstrated, validating current clinical practice. The management of acute mania requires antimanic medications that ensure safety and rapid suppression of the cognitive, behavioral, and psychotic symptoms occurring during episodes. The superior efficacy and speed of action of combinations have led some authors to propose the systematic use of a combination as a first line option [8]. It is therefore important to study the long-term effects of these drug combinations in terms of tolerance and preventing relapse.

Combination therapy and prevention to relapse

The primary goal of maintenance therapy is to achieve symptomatic and then functional remission and to prevent relapse of any pole, but mostly the acute pole [12]. Several recent studies have documented the superiority of combination products for the prophylactic treatment phase. Mood stabilizers have various profiles of efficacy and tolerability, suggesting that they could have complementary roles in long-term maintenance treatment and the prevention of relapse [39]. A recent review of randomized trials found that Li, lamotrigine (LAM), olanzapine (OLZ) and VPA, were each more effective than placebo at preventing relapse to any mood episode. Li and OLZ significantly reduced manic relapses [39].

Numerous studies, summarized in Table 2 [34,40-51], show that the time to relapse to any mood episode was longer under continuation of APA and Li or VPA treatment than Li or VPA monotherapy. These findings suggest that there is a long-term benefit in continuing APA as an adjunct to a mood stabilizer after sustained remission is achieved. Vieta et al. reported meta-analysis examining the efficacy of maintenance treatments for BD. Of the combination treatments studied, ziprasidone with Li or VPA and risperidone with Li or VPA significantly reduced the risk of a manic relapse, and only quetiapine with Li or VPA significantly reduced the risk for relapse at both the manic/mixed and depressed poles of BD

[52]. However, the continued use of a typical antipsychotic following remission from acute mania was associated, in the study by Zarate et al., with a shorter time to depressive relapse, more depressive symptoms, higher rates of dysphoria and Parkinsonism, and greater discontinuation rates. These findings imply that the continued use of typical antipsychotics following remission from mania might be detrimental for the depressive pole [50]. Thus, maintenance of APA after a manic phase is controversial: it may reduce the risk of manic relapse, but also shorten the time to depressive relapse. This option therefore needs to be considered in the light of the disease course and predominant polarity of each patient. Quetiapine might be a useful option in cases of depressive-predominant polarity. Combination treatment with aripiprazole in situations of addictive comorbidities in BD may be particularly beneficial [53]. An open study investigated replacing the previous antipsychotic treatment with aripiprazole in patients treated for BD or schizoaffective disorder who displayed signs of substance abuse; this treatment resulted in a significant reduction in the craving for alcohol and cocaine over a 3-month follow-up [54]. Finally, age at onset of BD has been proposed to be a prognostic marker of the response to treatment and should be considered for future treatment clinical trials [55].

Further studies are needed to confirm these various preliminary results and may contribute to the development of more personalized therapies for acute and maintenance manic phases.

- Table 2 about here -

In summary, the time to recurrence of any event (mania, depression, or mixed) in manic episode seems to be longer under combination maintenance treatment, especially with APA in combination with Li/VPA, than under placebo with Li/VPA. However, this notion is disputed

because the continued use of typical antipsychotics following remission from mania has been observed by Zarate and colleagues to be detrimental for the depressive pole [50]. Combination treatments can provide an effective long-term option for bipolar disorder to prevent recurrences of mania and/or depressive episodes but may lead to residual depressive symptoms. In addition to considerations of long-term effectiveness, the issues of tolerability and side-effect profile of combination treatments need to be addressed.

Tolerability and side-effect profile of combinations

Combining treatments can be advantageous as a result of therapeutic synergy; however, there are potential problems associated with the cumulative risk of adverse effects [56]. The decision to use a combination therapy should be made on the basis of the efficacy, tolerability, and safety of each medication and their specific combination for individual patients [57].

The meta-analysis of Cipriani et al. concluded that among antimanic drugs , risperidone, olanzapine and haloperidol are the best of the available options for the treatment of manic episodes [37]. Unfortunately, these results were obtained by pooling data from both monotherapy and combination studies, and no separate analysis of efficacy and acceptability of combined therapies alone is provided. The efficacy of a drug as an adjuvant can be assessed more reliably from analysis of its combination with placebo than with another active drug; the results of studies involving combinations of two or more drugs should therefore be interpreted with caution [58]. Although the efficacy of olanzapine is good, its tolerability profile is marked by a possible rapid weight gain and metabolic syndrome; these issues have led to the guidelines of WFSBP recommending decreased use of olanzapine [2].

There is insufficient data available about combination therapies and their tolerability profiles; Table 3 provides an overview of RCT reporting safety and tolerability data for various combinations [21-25,29,30,34,41,42,44,45,48].

- Table 3 about here -

The patterns of safety and tolerability differ between types of combination. The whole sample of combinations exhibited more side effects than monotherapy, and higher discontinuation rates due to adverse events (rate range of 1.9 to 17% for combination versus 0 to 13.3% for Li/VPA monotherapy). Weight gain is particularly significant for combinations including olanzapine (mean range of +2 to +3.04 kgs for combination versus -1.8 to +0.23 for Li/VPA monotherapy) or asenapine (mean of +3.5 kgs for combination versus 1.7 kgs for Li/VPA monotherapy) and to a lesser extent risperdal (mean range of +1.7 to +2.4 kgs for combination versus +0.5 for Li/VPA monotherapy). Combination of Li/VPA with quetiapine results in increased sedation (80% versus 33% for Li/VPA monotherapy), haloperidol (30% in combination versus 12% in Li/VPA monotherapy) and asenapine (14.6% in combination versus 5.6% in Li/VPA monotherapy). Combinations including aripiprazole may lead to a greater risk of akathysia (18.6% in combination versus 5.4% in Li/VPA monotherapy). Lastly, all the APA used in combination may be associated with tremor side effects (rate range of 6.0 to 17% for combination with APA versus 2.4 to 12.1% for Li/VPA monotherapy). A recent adjunction study indicates that addition of risperidone to a mood stabilizer has a negative effect on executive function and verbal learning, an effect not shared with quetiapine [59]. Further randomized controlled trials are required to confirm the findings of this preliminary study and the cognitive side effects of medications prescribed for maintenance treatment of bipolar I disorder. Lastly, the comparison reported by Brooks et al. in the Systematic

Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is of interest: they evaluated the safety and tolerability of APA polytherapy compared to APA monotherapy in 1,958 BD patients. One out of ten patients treated with APA was under APA polytherapy, and such polytherapy compared to APA monotherapy was associated with greater side effects and health service use but not with better clinical status or function [60]. Thus, the combination of APA with Li/VPA presents advantages in efficacy with moderate side effects, but APA polytherapy should be avoided because there is a substantial risk of side effects without a clear therapeutic benefit.

The primary therapeutic objective of maintenance therapy is to prevent relapse and recurrence of acute mood events. As patients are likely to receive maintenance treatment for long periods, the tolerability of these agents is an important consideration. One APA with Li/VPA combination shows the best efficacy with acceptable safety and tolerability. Specific adverse events, and in particular weight gain and sedation, need to be evaluated before initiating an adjunctive or combination therapy and to be monitored after its introduction.

CONCLUSION

The first-line approach to manic phases in all the guidelines we examined is monotherapy, with combination therapies being reserved for severe cases or as a second choice. In real-life practice, monotherapy is often not sufficient during acute and/or maintenance therapy. Consequently, most patients are administered combination therapies. There is currently no appropriate algorithm involving different combination treatments, the phase of the illness and specific clinical presentations despite the very common phenomenon of combined prescriptions. This review of literature leads us to suggest that combination therapy with APA and Li or VPA could be used as a first-line approach because it is more

effective than monotherapy for treatment during the acute phase. The use of combinations during maintenance phases requires prudence and careful consideration of tolerability and the safety profile. Each combination and should be evaluated on an individual basis. Future guidelines need to include suitable algorithm to help decision-making concerning the use of combination treatment.

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REFERENCES

1. Rosa AR, Franco C, Martínez-Aran A, Sánchez-Moreno J, Reinares M, Salamero M, et al. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom. 2008;77(6):390-2.

2. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller H-J, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J. Biol. Psychiatry. 2009;10(2):85-116.

3. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. J. Psychopharmacol. (Oxford). 2009;23(4):346-88.

4. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11(3):225-55.

5. Malhi GS, Adams D, Lampe L, Paton M, O'Connor N, Newton LA, et al. Clinical practice recommendations for bipolar disorder. Acta Psychiatr Scand Suppl. 2009;(439):27-46.

6. NICE. Bipolar disorder [Internet]. NICE. 2006 juill 26 ;Available from: http://www.nice.org.uk/

7. Lim PZ, Tunis SL, Edell WS, Jensik SE, Tohen M. Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines. Bipolar Disord. 2001;3(4):165-73.

8. Nivoli AMA, Murru A, Goikolea JM, Crespo JM, Montes JM, González-Pinto A, et al. New treatment guidelines for acute bipolar mania: A critical review. Journal of Affective Disorders 2012;140(2):125-41.

9. Wolfsperger M, Greil W, Rössler W, Grohmann R. Pharmacological treatment of acute mania in psychiatric in-patients between 1994 and 2004. J Affect Disord. 2007;99(1-3):9-17.

10. Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry. 2000;61(1):9-15.

11. Haro JM, Reed C, Gonzalez-Pinto A, Novick D, Bertsch J, Vieta E. 2-Year course of bipolar disorder type I patients in outpatient care: factors associated with remission and functional recovery. Eur Neuropsychopharmacol. 2011;21(4):287-93.

12. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry. 2002;159(4 Suppl):1-50.

13. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. J Affect Disord. 1980;2(4):279-88.

14. Klein E, Bental E, Lerer B, Belmaker RH. Carbamazepine and haloperidol v placebo and haloperidol in excited psychoses. A controlled study. Arch. Gen. Psychiatry. 1984;41(2):165-70.

15. Muller AA, Stoll KD. Carbamazepine and oxcarbazepine in the treatment of manic syndromes: studies in Germany. In: Emrich HM, Okuma T, Muller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, Netherlands: Excerpta Medica; 1984:134-147.

16. Desai NG, Gangadhar BN, Channabasavanna SM. Shetty KT. Carbamazepine hastens therapeutic action of lithium in mania. Proceedings Inter-national Conference on New Directions in Affective Disorders. Jerusalem, Israel, 1987:97.

17. Möller HJ, Kissling W, Riehl T, Bäuml J, Binz U, Wendt G. Doubleblind evaluation of the antimanic properties of carbamazepine as a comedication to haloperidol. Prog. Neuropsychopharmacol. Biol. Psychiatry. 1989;13(1-2):127-36.

18. Anand, A., Oren, DA, Berman, RM, Cappiello. A., & Charney, DS (1999). Lamotrigine treatment of lithium failure outpatient mania: a double-blind, placebo-controlled trial. In

JC Scares & S. Gershon (Eds.), Abstract Book on 3rd international conference on Bipolar disorder (p.23). Pittsburgh, PA. Copenhagen: Munksgaard.

19. Müller-Oerlinghausen B, Retzow A, Henn FA, Giedke H, Walden J. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. European Valproate Mania Study Group. J Clin Psychopharmacol. 2000;20(2):195-203.

20. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord. 2000;2(3 Pt 2):249-55.

21. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry. 2002;159(7):1146-54.

22. Tohen M, Chengappa KNR, Suppes T, Zarate CA Jr, Calabrese JR, Bowden CL, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch. Gen. Psychiatry. 2002;59(1):62-9.

23. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002;41(10):1216-23.

24. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. Br J Psychiatry. 2003;182:141-7.

25. Sachs G, Chengappa KNR, Suppes T, Mullen JA, Brecher M, Devine NA, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2004;6(3):213-23.

26. McIntyre RS, Konarski JZ, Jones M, Paulsson B. Quetiapine in the treatment of acute bipolar mania: efficacy across a broad range of symptoms. J Affect Disord. 2007;100 Suppl 1:S5-14.

27. Yatham LN, Vieta E, Young AH, Möller H-J, Paulsson B, Vågerö M. A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. Int Clin Psychopharmacol. 2007;22(4):212-20.

28. Sussman N, Mullen J, Paulsson B, Vågerö M. Rates of remission/euthymia with quetiapine in combination with lithium/divalproex for the treatment of acute mania. J Affect Disord. 2007;100 Suppl 1:S55-63.

29. Vieta E, T'joen C, McQuade RD, Carson WH Jr, Marcus RN, Sanchez R, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. Am J Psychiatry. 2008;165(10):1316-25.

30. Tohen M, Bowden CL, Smulevich AB, Bergstrom R, Quinlan T, Osuntokun O, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry. 2008;192(2):135-43.

31. Juruena MF, Ottoni GL, Machado-Vieira R, Carneiro RM, Weingarthner N, Marquardt AR, et al. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2009;33(1):94-9.

32. Amrollahi Z, Rezaei F, Salehi B, Modabbernia A-H, Maroufi A, Esfandiari G-R, et al. Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. J Affect Disord. 2011;129(1-3):327-31.

33. Berwaerts J, Lane R, Nuamah IF, Lim P, Remmerie B, Hough DW. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. J Affect Disord. 2011;129(1-3):252-60.

34. Szegedi A, Calabrese JR, Stet L, Mackle M, Zhao J, Panagides J. Asenapine as Adjunctive Treatment for Acute Mania Associated With Bipolar Disorder: Results of a 12-Week Core Study and 40-Week Extension. J Clin Psychopharmacol. 2012;32(1):46-55.

35. Ouyang W-C, Hsu M-C, Yeh I-N, Kuo C-C. Efficacy and safety of combination of risperidone and haloperidol with divalproate in patients with acute mania. Int J Psychiatry Clin Pract. 2012;16(3):178-88.

36. Cookson J. Use of antipsychotic drugs and lithium in mania. Br J Psychiatry. 2001;178(Suppl 41):S148-156.

37. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378(9799):1306-15.

38. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. Bipolar Disord. 2007;9(6):551-60.

39. Smith LA, Cornelius V, Warnock A, Bell A, Young AH. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disord. 2007;9(4):394-412.

40. Geddes JR, Goodwin GM, Rendell J, Azorin J-M, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375(9712):385-95.

41. Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord. 2008;109(3):251-63.

42. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry. 2009;166(4):476-88.

43. Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR. Quetiapine and classical mood stabilizers in the long-term treatment of Bipolar Disorder: a 4-year follow-up naturalistic study. J Affect Disord. 2008;110(1-2):135-41.

44. Tohen M, Chengappa KNR, Suppes T, Baker RW, Zarate CA, Bowden CL, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry. 2004;184:337-45.

45. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry. 2010;71(2):130-7.

46. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord. 2011;13(2):133-44.

47. Woo YS, Bahk W-M, Chung MY, Kim D-H, Yoon B-H, Lee JH, et al. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. Hum Psychopharmacol. 2011;26(8):543-53.

48. Vieta E, Owen R, Baudelet C, McQuade RD, Sanchez R, Marcus RN. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. Curr Med Res Opin. 2010;26(6):1485-96.

49. Carlson BX, Ketter TA, Sun W, Timko K, McQuade RD, Sanchez R, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disord. 2012;14(1):41-53.

50. Zarate CA. Double-Blind Comparison of the Continued Use of Antipsychotic Treatment Versus Its Discontinuation in Remitted Manic Patients. Am J Psychiatry. 2004;161(1):169-71.

51. Vieta E, Cruz N, García-Campayo J, de Arce R, Manuel Crespo J, Vallès V, et al. A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int. J. Neuropsychopharmacol. 2008;11(4):445-52.

52. Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. Int. J. Neuropsychopharmacol. 2011;14(8):1029-49.

53. Geoffroy PA, Goddefroy G, Rolland B, Cottencin O. Efficacy of aripiprazole in comorbid addiction in bipolar disorder. CNS Neurosci Ther. 2012;18(4):359-60.

54. Brown ES, Jeffress J, Liggin JDM, Garza M, Beard L. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. J Clin Psychiatry. 2005;66(6):756-60.

55. Geoffroy PA, Etain B, Scott J, Henry C, Jamain S, Leboyer M, et al. Clinical characteristics, biomarkers and therapeutic relevance of early-onset bipolar disorder. J Physiol Paris. In press.

56. Ketter TA. Treating bipolar disorder: monotherapy versus combination therapy. J Clin Psychiatry. 2009;70(2):e42.

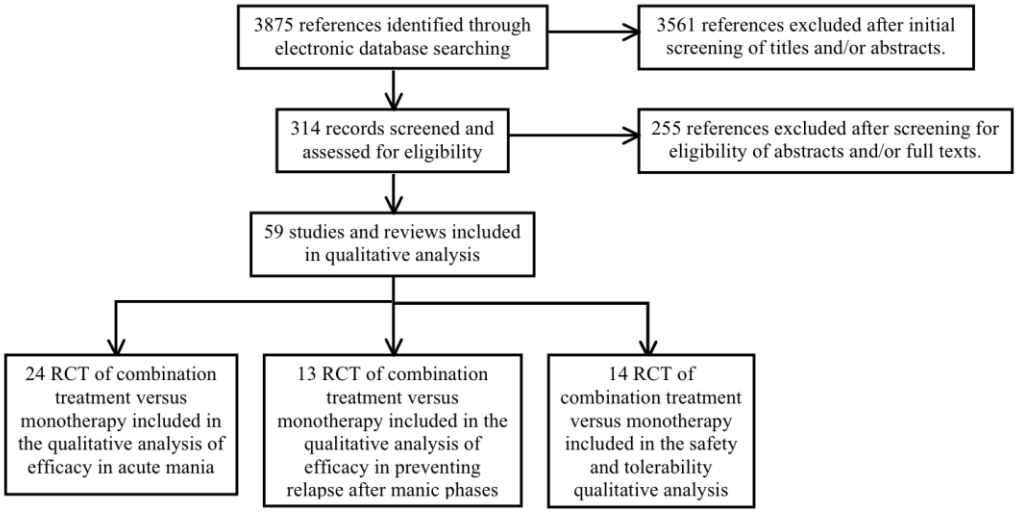
57. Ketter TA. Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. J Clin Psychiatry. 2008;69 Suppl 5:9-15.

58. Berk M, Malhi GS. Should antipsychotics take pole position in mania treatment? Lancet. 2011;378(9799):1279-81.

59. Kozicky J-M, Torres IJ, Bond DJ, Lam RW, Yatham LN. Comparison of neuropsychological effects of adjunctive risperidone or quetiapine in euthymic patients with bipolar I disorder. Int Clin Psychopharmacol. 2012;27(2):91-9.

60. Brooks JO 3rd, Goldberg JF, Ketter TA, Miklowitz DJ, Calabrese JR, Bowden CL, et al. Safety and tolerability associated with second-generation antipsychotic polytherapy in bipolar disorder: findings from the Systematic Treatment Enhancement Program for Bipolar Disorder. J Clin Psychiatry. 2011;72(2):240-7.

Figure 1: Study selection for the qualitative analysis of combination treatment versus monotherapy in bipolar disorder.



RCT = randomized controlled trial

Table 1: A review of RCT of combination therapy in the treatment of manic phases.

Study	Duration (days)	Combination treatment (Number of subjects)	Outcome (efficacy assessed by changes in manic symptoms)
Garfinkel et al., 1980	21	Li + PBO (7) HAL + PBO (7) Li + HAL (7)	HAL + PBO = HAL + Li > PBO + Li
Klein et al., 1984	35	CBZ + HAL (14) PBO + HAL (13)	CBZ + HAL > PBO + HAL
Müller & Stoll, 1984	21	CBZ + HAL (6) PBO + HAL	CBZ + HAL > PBO + HAL
Desai et al., 1987	28	CBZ + Li (5) PBO + Li	CBZ + Li > PBO + Li
Möller et al., 1989	21	CBZ + HAL (11) PBO + HAL (9)	CBZ + HAL = PBO + HAL Smaller amount of additional LEV in the CBZ + HAL group evidencing the antimanic effect of the combination
Anand et al., 1999	56	LAM + Li (8) PBO + Li (8)	LAM + Li = PBO + Li
Müller-Oerlinghausen et al., 2000	21	VPA + SND (69) PBO + SND (67)	VPA + SND > PBO + SND VPA + SND allows the administration of fewer BZD and/or SND
Pande et al., 2000	70	GBP + MS (54) PBO + MS (59)	GBP + MS < PBO + MS
Sachs et al., 2002	21	RSP + MS (52) HAL + MS (53) PBO + MS (51)	RSP + MS = HAL + MS > PBO + MS
Tohen et al., 2002	42	OLZ + MS (220) PBO + MS (114)	OLZ + MS > PBO + MS
Delbello et al., 2002	42	QTP + VPA (15) PBO + VPA (15)	QTP + VPA > PBO + VPA
Yatham et al., 2003	21	RSP + MS (75) PBO + MS (75)	Post hoc analysis excluding CBZ-treated patients revealed significant: RSP + MS > PBO + MS
Sachs et al., 2004	21	QTP + MS (91) PBO + MS (100)	QTP + MS > PBO + MS
Akhondzadeh et al., 2006	56	ALP + HAL + Li (38) PBO + HAL + Li (37)	ALP + HAL + Li > PBO + HAL + Li
McIntyre et al., 2007	84	QTP + MS (197) PBO + MS (205)	QTP + MS > PBO + MS
Yatham et al., 2007	42	QTP + MS (104) PBO + MS (96)	QTP + MS > PBO + MS
Sussmam et al., 2007	42	QTP + MS (197) PBO + MS (205)	QTP + MS > PBO + MS
Vieta et al., 2008	42	ARI + MS (253) PBO + MS (131)	ARI + MS > PBO + MS
Tohen et al., 2008	42	OLZ + CBZ (58) PBO + CBZ (60)	OLZ + CBZ = PBO + CBZ
Juruena et al., 2009	56	OXC + Li (26) CBZ + Li (26)	OXC + Li > CBZ + Li
Amrollahi et al., 2011	42	TXF + Li (20) PBO + Li (20)	TXF + Li > PBO + Li
Berwaerts et al., 2011	84	PER + MS (197) PBO + MS (205)	PER + MS = PBO + MS
Szegedi et al., 2012	52	ASE + MS (158) PBO + MS (166)	ASE + MS > PBO + MS
Ouyang et al., 2012	21	RSP + VPA (22) HAL + VPA (19)	RSP + VPA > HAL + VPA

> = more effective; ALP = allopurinol; ARI = aripiprazole; ASE = asenapine; BZD = benzodiazepines; CBZ = carbamazepine; GBP = gabapentine; HAL = haloperidol; LAM = lamotrigine; LEV = levomepromazine; Li = lithium; MS = mood-stabilizer (lithium or valproate); OLZ = olanzapine; PBO = placebo; PER = paliperidone extended-release; QTP = quetiapine; RSP = risperidone; SND = standard neuroleptic drug; TXF = tamoxifen; VPA = valproate.
RCT = randomized controlled trial.

Table 2: Summary of RCT of combination therapy in manic phases and measure of time to relapse to any mood episode.

Study	Combination	Combination (=C) or Adjunction* (=A)	Duration (w=weeks) (m=months) (y=year)	Outcome (relapse prevention)
Geddes et al., 2010	Li + VPA PBO + Li PBO + VPA	C	24 m	Li + VPA = PBO + Li > PBO + VPA
Vieta et al., 2008	QTP + Li/VPA PBO + Li/VPA	C	104 w	QTP + Li/VPA > PBO + Li/VPA
Suppes et al., 2009	QTP + Li/VPA PBO + Li/VPA	C	104 w	QTP + Li/VPA > PBO + Li/VPA
Altamura et al., 2008	QTP + Li QTP + VPA PBO + QTP PBO + Li PBO + VPA PBO + LAM	C	4 y	QTP + Li > QTP + VPA > PBO + Li > PBO + LAM > PBO + VPA > PBO + QTP
Tohen et al., 2004	OLZ + Li/VPA PBO + Li/VPA	C	18 m	OLZ + Li/VPA > PBO + Li/VPA for syndromic but not functional remission
Bowden et al., 2010	Zip + Li/VPA PBO + Li/VPA	C	6 m	Zip + Li/VPA > PBO + Li/VPA
Szegedi et al., 2012	ASE + Li/VPA PBO + Li/VPA	A (≥2 w)	52 w	ASE + Li/VPA > PBO + Li/VPA
Marcus et al., 2011	ARI + Li/VPA PBO + Li/VPA	A (≥2 w)	52 w	ARI + Li/VPA > PBO + Li/VPA
Woo et al., 2011	ARI + VPA PBO + VPA	C	6 m	NS
Vieta et al., 2010	ARI + Li/VPA PBO + Li/VPA	C	46 w	ARI + Li/VPA > PBO + Li/VPA
Carlson et al., 2012	ARI + LAM PBO + LAM	C	52 w	NS
Zarate et al., 2004	PPZ + Li/VPA/CBZ PBO + Li/VPA/CBZ	C	6 m	PPZ + Li/VPA/CBZ < PBO + Li/VPA/CBZ
Vieta et al., 2008	OXC + Li PBO + Li	A (NR)	52 w	NS

**For studies with adjunction, time in weeks before addition is indicated in parentheses.*

> = Combination is more effective than monotherapy in terms of relapse; ARI = aripiprazole; ASE: asenapine; BZD = benzodiazepines; CBZ = carbamazepine; LAM = lamotrigine; Li = lithium; NS = not statistically significant; NR = not reported; OLZ = olanzapine; OXC = oxcarbazepine PBO = placebo; PPZ = perphenazine; QTP = quetiapine; RSP = risperidone; VPA = valproate; Zip = ziprasidone.

Table 3: Tolerability of combination therapy for the treatment of manic phases.

Study	Combination treatment (n)	Discontinuation rates due to adverse events (%)	Mean change in weight (kg)	Weight gain*	Sedation / Somnolence*	EPS* (Extra Pyramidal Symptoms)	Tremor*	Akathisia*	Depressive symptoms*	Insomnia*
Sachs et al., 2002	RSP + MS (52)	3.8	+2.4	X	X					
	HAL + MS (53)	1.9	+0.13		X	X	X			
	PBO + MS (51)	3.9	+0.5							
Yatham et al., 2003	RSP + MS (75)	NR	+1.7							
	PBO + MS (75)	NR	+0.5							
Tohen et al., 2002	OLZ + MS (220)	10.9	+3.04	X	X		X			
	PBO + MS (114)	1.7	+0.23						X	
Tohen et al., 2004	OLZ + MS (51)	NR	+2.0	X						
	PBO + MS (48)		-1.8							X
Delbello et al., 2002	QTP + VPA (15)	6.6	NR		X					
	PBO + VPA (15)	0	NR							
Vieta et al., 2008	QTP + MS (213)	2.4	+0.5		X					
	PBO + MS (134)	3	-1.9							X
Suppes et al., 2009	QTP + MS (253)	11.3	+0.5	X	X					
	PBO + MS (131)	2.6	-2.0							
Sachs et al., 2004	QTP + MS (91)	5	NR		X					
	PBO + MS (100)	6	NR							
Vieta et al., 2008	ARI + MS (253)	9	+0.55					X		
	PBO + MS (131)	5	+0.23							
Marcus et al., 2011	ARI + MS (168)	11.4	+1.1				X			
	PBO + MS (169)	9	+0.6							
Vieta et al., 2010	ARI + Li (55)	17	+2.3							
	ARI + VPA (91)	12.6	+2.0							
Carlson et al., 2012	ARI + LAM (178)	8	+0.43					X		
	PBO + LAM (173)	7.3	-1.81							X
Bowden et al., 2010	Zip + MS (127)	8.7	-0.8				X			
	PBO + MS (113)	13.3	+0.5							X
Szegedi et al., 2012	ASE + MS (158)	NR	+3.5	X	X				X	
	PBO + MS (166)	NR	+1.7							

Only significant and reported emergent adverse events are reported from original studies.

* statistically significant symptom measure; > = more effective; ARI = aripiprazole; ASE = asenapine; BZD = benzodiazepines; CBZ = carbamazepine; GBP = gabapentine; HAL = haloperidol; LAM = lamotrigine; LEV = levomepromazine; Li = lithium; MS = mood-stabilizer (lithium or valproate); NR = not reported; OLZ = olanzapine; PBO = placebo; QTP = quetiapine; RSP = risperidone; SND = standard neuroleptic drug; VPA = valproate.