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REVIEW

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Combination Therapy for Manic Phases: A Critical Review of a Common Practice

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SUMMARY

All relevant guidelines 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 risperidone are associated with weight gain, those including quetiapine, haloperidol and asenapine with sedation, and those including aripiprazole with akathisia. 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.

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) or another 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 patients with BD 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 patients with BD 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 relevant randomized controlled studies.

Materials and 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

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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 11th, 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).

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.

Guidelines [2–6] favor monotherapy as the first-line approach, for safety and practicability reasons, and recommend making best use of the dose range available for a given medication, since combined treatment is likely to be associated with 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 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 patients with BD. 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.

One review reports that antipsychotic medication is widely used, being prescribed to between 72% and 92% of patients with

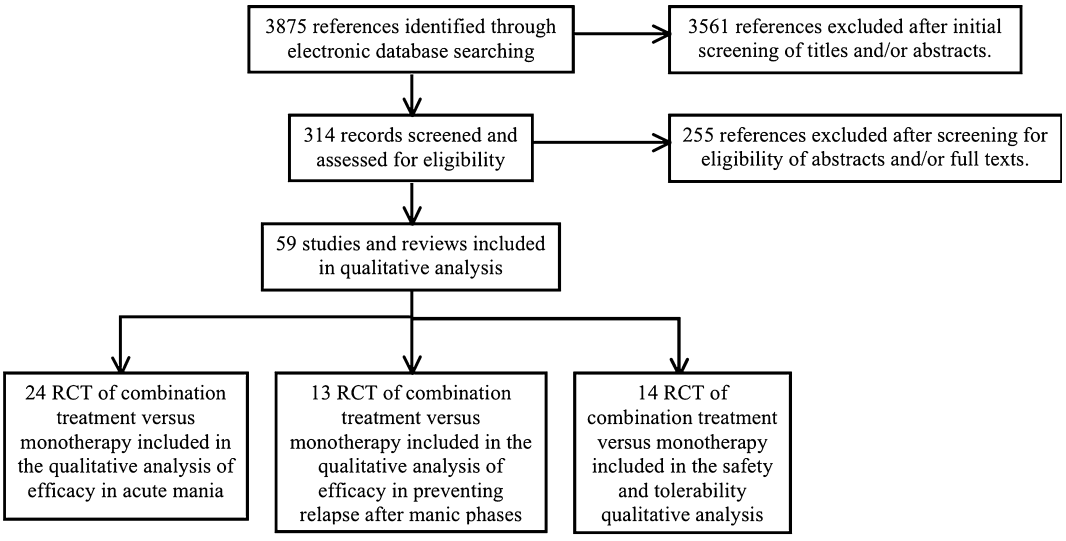

Figure 1 Study selection for the qualitative analysis of combination treatment versus monotherapy in bipolar disorder. RCT, randomized controlled trial.

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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.

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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 when 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 index 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 of 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.

In summary, the time to recurrence of any event (mania, depression, or mixed) after a 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].

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

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].

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 vs. 0 to 13.3% for Li/VPA monotherapy). Weight gain is particularly significant for combinations including olanzapine (mean range of + 2 to + 3.04 kg for combination vs. −1.8 to + 0.23 for Li/VPA monotherapy) or asenapine (mean of + 3.5 kg for combination vs. 1.7 kg for Li/VPA monotherapy) and to a lesser extent risperidone (mean range of + 1.7 to + 2.4 kg for combination vs. +0.5 for Li/VPA monotherapy). Combination of Li/VPA with quetiapine results in increased sedation (80% vs. 33% for Li/VPA monotherapy), haloperidol (30% in combination vs. 12% in Li/VPA monotherapy) and asenapine (14.6% in combination vs. 5.6% in Li/VPA monotherapy). Combinations including aripiprazole may lead to a greater risk of akathisia (18.6% in combination vs. 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 vs. 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 with APA monotherapy in 1,958 patients with BD. One of ten patients treated with APA was under APA polytherapy, and such polytherapy compared with APA monotherapy was

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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.

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associated with greater side effects and health service use but not with better clinical status or functioning [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 a careful consideration of tolerability and the safety profile. Each combination 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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Conflict of Interest

PAG declares no conflict of interest regarding the present study and has received no compensation for professional services in the 2 years prior to submission of this paper.

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