

# Association of antipsychotics and mood stabilizers for treatment of mania

*L'associazione di farmaci antipsicotici e stabilizzanti dell'umore nel trattamento della mania*

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## Summary

### Objective

Given the complex nature and frequent comorbidities of bipolar disorder (BD), polypharmacy is often used to achieve and maintain remission. In clinical practice, this is frequently the rule rather than the exception. Although research on BD uncommonly involves controlled clinical studies for combination therapies, clinicians nonetheless utilize polypharmacy as the best clinical treatment. A selective review of the literature for the best use of combination therapies, chiefly antipsychotics and mood stabilizers, has been carried out in order to offer rational indications.

### Method

Findings from studies on the concomitant use of antipsychotics and mood stabilizers have been reported for the different phases of mania: acute agitation, acute phase and remission phase. Guideline recommendations have also been reported.

### Results

Second generation antipsychotics (SGAs), particularly if avail-

able in intramuscular and oral formulations, give clinicians the possibility of continuity of pharmacotherapy, in terms of efficacy and tolerability.

Association of MSs and SGAs in the treatment of mania increases efficacy compared with monotherapy in all the phases of the disorder. Accordingly, combination therapy should be the treatment of choice, particularly for severe manic and treatment-resistant episodes.

### Conclusions

Several combinations of MSs with SGAs appear to be safe and effective, and provide good results as often reflected in published data. Polypharmacy, as well as polypsychotherapy, and complex combination therapy, may be the best means to balance the complexity and comorbidities of BD. However, clinical vigilance and safety monitoring are relevant aspects when polypharmacy is used.

### Key words

Polypharmacy • First generation antipsychotics • Second generation antipsychotics • Mood stabilizers • Drug interactions • Bipolar Disorder

## Occam's razor and the psychopharmacology of mania

Occam's razor is the law of parsimony, which is often invoked in the clinic for a single diagnosis that could account for all symptoms. The principle of diagnostic parsimony can be problematic for psychiatric disorders, and even more for drug treatment than for aetiologically-based diseases.

Although parsimony can be the ideal goal of a psychotropic treatment, such a 'rule' is scarcely suitable in routine clinical practice. Monotherapy can limit drug interactions and unwanted effects, as well as improve compliance; indeed, the complex symptomatology of the disorder and its resistance to treatment drive the clinician to prescribe polypharmacy. This condition is frequently

observed in bipolar disorder (BD), both when the acute manic symptomatology requires urgent treatment, as well as in the remission phase.

Monotherapy with a mood stabilizer can be used as initial treatment for drug naive patients presenting with mild to moderate symptoms, but this is not a frequent situation<sup>1</sup>. Given the complex nature and frequent comorbidities of the disorder, polypharmacy is often used to fulfill the goal of achieving and maintaining remission. Unfortunately, research on BD does not frequently involve controlled clinical studies for complex combination therapy, but this has not hampered clinicians from using polypharmacy as the best clinical treatment<sup>2,3</sup>. In this regard, the use of second generation antipsychotics in BD has opened new possibilities for therapy.

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## Acute phase of mania: adding a mood stabilizer to antipsychotic treatment

### *Acute agitation*

Acute agitation, with the risk of physical destructiveness, threatening gestures and language, and lack of compliance with oral therapy, is common in the acute phase of mania. In this phase, treatment characterized by a rapid onset of action and possibly intramuscular administration may be of particular benefit.

Benzodiazepines and antipsychotics, frequently used in association, are well tolerated<sup>4</sup>. First generation antipsychotics (FGAs) are generally less well tolerated than second generation antipsychotics (SGAs) because of extrapyramidal symptoms (EPS), as patients with BD more susceptible, and over-sedation that can hinder physician/patient interaction, thus making it difficult to assess the patient's status<sup>5</sup>. The occurrence of adverse effects can affect long-term patient compliance, which should be taken into consideration early in therapy. Rapid sedation by parenteral antipsychotics associated with benzodiazepines in acute settings, so-called 'chemical restraint', is no longer endorsed by clinical guidelines which suggesting calming rather than sedating the suitable management of agitation<sup>6,7</sup>.

The SGAs are now used as first-line agents<sup>8,9</sup>. Intramuscular (IM) formulations of aripiprazole and ziprasidone have been shown to improve symptoms of agitation through a calming effect with a low risk of over-sedation that provide practical clinical benefits<sup>10-12</sup>. This calming effect seen with IM olanzapine has been observed paralleled by a higher incidence of somnolence<sup>8</sup>. Among SGAs, aripiprazole is pharmacologically distinct: its novel pharmaco-dynamic profile acts through dopamine-serotonin system stabilization by partial agonism to minimize unwanted effects<sup>13,14</sup>.

Due to the characteristics of mood stabilizers (MSs), they are not suitable in this phase. As full clinical recovery from acute mania typically requires many weeks, when the acute agitation is overcome, the need for further treatment is warranted. Nonetheless, in this early phase, an intensive effort of therapeutic reasoning by the psychiatrist is necessary, anticipating the treatment needs of the next phases when the choice of MS administration will be made. Because in clinical reality antipsychotic therapy administered in acute phase can be continued if well tolerated and effective, this first choice during acute agitation treatment has to be made carefully.

### *Beyond urgency: transition to oral formulations*

As the treatment of mania needs to anticipate the future course of the illness, selection of the most appropriate

IM treatment is relevant for the next therapy even in the most acute phase, as this choice is critical for maintaining efficacy and tolerability. The IM dose of antipsychotic should therefore be personalized in order to ensure minimal adverse effects, as a result of too low or high dosing, when switching to an equivalent oral dose for long-term treatment<sup>6</sup>.

Since SGAs are now available in IM as well as oral formulations, clinicians have the possibility of *continuity* in drug administration, in terms of efficacy and tolerability, avoiding the effects of a switch from FGAs that may interfere with long-term patient compliance<sup>15</sup>.

### *Acute phase treatment*

The first, and for decades the only, drugs with regulatory approval for acute mania have been lithium and chlorpromazine. It is likely not by chance that these two drugs have different profiles, i.e. a MS and an antipsychotic were approved and licensed for mania, but because of their frequent use in association. Although with limited support from randomized controlled trials (RCTs), other FGAs, potent benzodiazepines and anticonvulsants, including carbamazepine and valproate, have also been empirically used<sup>16</sup>. Due to their unfavourable risks of short- and long-term adverse effects, FGAs are no longer the first choice for treatment of acute mania. Haloperidol, even if widely used and studied but never licensed for the treatment of mania by Food and Drug Administration (FDA), has been associated with severe cases, although disputable, of neurotoxicity in association with lithium<sup>17</sup>. Currently, all SGAs (except clozapine), lithium, valproate and carbamazepine have been approved by the FDA and similar European agencies (e.g. European Medicines Agency, EMA) for treatment of acute bipolar mania.

Comprehensive meta-analyses of RCTs of treatments for acute bipolar mania indicate that antipsychotic agents (SGAs or haloperidol) have superior efficacy and a more rapid action than MSs<sup>18,19</sup>. The few available direct comparisons favour SGAs over MSs for acute mania, even though the two groups of drugs show similar pooled effect sizes compared with placebo. The faster antipsychotic speed of clinical action and the normally short duration of trials do not generally favour MSs. Moreover, some SGAs also present considerable adverse metabolic effects in the long-term<sup>16</sup>. For example, olanzapine showed higher response rates and lower rates of dropout due to inefficacy, but higher rates of dropout due to adverse events, and its potential advantages in efficacy are counteracted by a higher rate of adverse effects. For ziprasidone, in contrast, there is no evidence of higher efficacy as an add-on treatment to MSs<sup>18</sup>. Quetiapine treatment for acute mania demonstrated efficacy in the majority of studies. Consideration however of debatable

efficacy robustness and cost could not suggest its use as first-line therapy, although it may be useful in case of sensitivity to EPS<sup>20</sup>.

On the other hand, a randomized, double-blind, placebo- and lithium-controlled study showed that aripiprazole provided improvement of acute mania within 2 days, that continued over 3 weeks and was sustained, similar to lithium, over 12 weeks; treatment was well-tolerated and the average overall weight gain was similar to placebo<sup>21</sup>.

Even if all these issues make it difficult to conclude that one drug or drug class is superior to another, the superiority of combination treatment over monotherapy in treating acute mania has been clearly demonstrated. Consistently, combination therapy, with controlled studies available for aripiprazole<sup>22</sup>, risperidone, olanzapine and quetiapine, shows significantly greater efficacy in combination<sup>23</sup>, with response rates exceeding those of lithium or valproate.

### Features of the manic phase

Different drug efficacy has been observed in manic phases with different features. The efficacy of treatment has been found to be different in patients with psychotic symptoms<sup>24,25</sup>. The efficacy was, however, not found to be different in patients with or without psychotic symptoms in other studies<sup>18</sup>. Placebo-controlled trials reporting outcomes of treatment in patients with rapid cycling concluded that aripiprazole and olanzapine are more efficacious<sup>26,27</sup>. In RCTs vs. placebo, aripiprazole had significantly greater efficacy for the treatment of BD patients in acute manic or mixed episodes<sup>28</sup>. Combination of olanzapine with MSs was more efficacious than MSs alone in patients with mixed episodes<sup>29</sup>.

On the other hand, the use of FGAs, even if effective in controlling acute psychotic mixed-mania, especially if administered in high dose, may exacerbate dysphoric or depressive symptoms, and their use should be avoided<sup>30</sup>.

### Summary

In clinical practice, driven by the urgency to treat the patient, in addition to pressures of time and costs, more than one drug is used to bring mania under control as quickly as possible, usually a combination of MSs and SGAs<sup>31</sup>. Other motivations of this empirical practice to add MSs to the antipsychotic treatment of acute mania can be the established neuroprotective and neurotrophic effects of MSs<sup>32,33</sup>, as well as the possibility to protect against a switch into depression<sup>34</sup>.

Association of MSs to SGAs in treatment of acute mania increases efficacy compared with monotherapy in improving acute symptoms, as indicated by greater reductions in mania scores, higher response rates, and fewer

dropouts due to inefficacy<sup>18,19</sup>. Based on these results, combination treatment with a SGA and MS should be the treatment of choice, in particular for severe manic episodes.

### The maintenance phase: adding an antipsychotic to a mood stabilizer

Because BD is a recurrent illness, long-term prophylactic/maintenance treatment is recommended. Patients generally receive maintenance treatment for extensive periods of time in order to prevent relapse and recurrence of acute mood events, and thus the tolerability of the drugs used is an important issue.

The evidence for best maintenance treatment of BD is changing and conflicting<sup>7,35-37</sup>.

Comprehensive analyses and meta-analyses have been conducted to determine the efficacy of pharmacological therapy in maintenance treatment of BD using evidence from independent clinical trials<sup>38,39</sup>. There are several available options for the long-term treatment, with considerable variations in the efficacy profile. The long-term efficacy of lithium and divalproex has been confirmed, particularly in combination<sup>40</sup>, while neither lamotrigine nor oxcarbazepine have shown evidence to support their use as monotherapy<sup>41,42</sup>. SGAs, such as aripiprazole, olanzapine, quetiapine and risperidone are effective in preventing manic/mixed relapses<sup>39</sup>.

For combination therapies, ziprasidone + lithium/divalproex<sup>43</sup> and risperidone + lithium/divalproex significantly reduced the risk of a manic relapse<sup>44,45</sup>, but only quetiapine + lithium/divalproex<sup>42,46</sup> significantly reduced the risk for relapse at both the manic/mixed and depressed poles of bipolar illness. In a 6-month study, aripiprazole was more effective than placebo in preventing mood episodes<sup>47</sup>. Adjunctive aripiprazole in subjects with inadequate response to lithium or valproate monotherapy was efficacious and well tolerated for long-term maintenance treatment of patients with BD, with no clinically significant change in metabolic parameters in the stabilisation phase or randomized phase during a one-year study<sup>48</sup>. On the other hand, one study failed to demonstrate any significant advantage of olanzapine + lithium/valproate vs lithium/valproate monotherapy in the majority of study endpoints, such as time to syndromic relapse into mania or depression with greater weight gain compared with monotherapy<sup>25</sup>. Drug interaction must also be considered, since concurrent use of valproate has been found significantly decrease the concentrations of olanzapine to an extent comparable with smoking<sup>49</sup>.

The efficacy of several interventions has been demonstrated, which can therefore be considered as appropriate options in maintenance treatment, although their efficacy

in clinical use needs to be balanced against safety and tolerability issues during long-term use.

### Summary

Successful maintenance therapy is not simple; it is however difficult to compare and interpret the available treatments. The increase of the time to recurrence is a crucial aim, since each relapse makes another relapse more likely. In this regard, SGAs in association with MSs can now be considered as first-line treatment even for moderately-ill patients with mania.

### Treatment resistance

The response of BD to established treatments for acute mania and maintenance is frequently inadequate, with many patients either not responding or showing poor compliance. Even under optimal maintenance conditions patients often report chronic symptoms and multiple episodes of recurrence, which thereby reduce the euthymic periods determining marked functional disability. Even today with the availability of multiple treatment options resistance remains a central problem<sup>50 51</sup>.

First line intervention is optimization of phase-specific, evidence-based treatment<sup>52</sup>. For mania, discontinued antidepressant therapy, lithium and divalproex are often used; addition of an atypical antipsychotic may have greater efficacy in severe mania: evidence-based efficacy in acute mania studies has been demonstrated for monotherapy with each of the atypical antipsychotics, usually at the commonly-used dosages for schizophrenia<sup>24 53</sup>.

In the case of failure, combination of multiple agents is the clinical strategy for treatment-resistant bipolar patients. However, except for acute mania, for which the association of MS with SGA is considered optimal treatment, standard treatment combinations have not been supported by controlled studies. These drug associations include higher doses of an atypical antipsychotic, lithium with divalproex or two anticonvulsants according to response unless limited by adverse effects. The most commonly recommended nonstandard treatments for treatment-resistant mania include high-dose thyroid augmentation, clozapine, calcium channel blockers and electroconvulsive therapy (ECT)<sup>52 54 55</sup>. A combination of clozapine and ECT has also been suggested<sup>56</sup>. Adjunctive psychotherapies such as education and enhancing coping strategies should also be considered.

Decisions about the choice of medications as well as dosing require clinical judgment because of the scarce evidence to drive decisions. Consideration of comorbid conditions, such as substance abuse, is needed to enhance stability. Evidence has been presented that com-

bination treatment of agents that failed in monotherapy may be effective<sup>57</sup>.

### Treatment of residual symptoms

Apparently less worrying than resistant patients are those who do not fully respond to treatment, showing residual symptoms. Residual mood symptoms in the recovery phase appear to be a powerful predictor of recurrence, both for depressive or manic/hypomanic subsyndromal symptoms. This condition should therefore be considered and treated until no symptoms are present<sup>51 58</sup>. In particular, residual manic symptoms seem to confer a higher risk for both manic or depressive recurrences. Again, the association of SGAs and MSs should be considered for these patients.

With such predictors of the risk of recurrence, these patients deserve intensive follow-up and treatment targeted to full remission<sup>59</sup>. The study of how these predictors may moderate or mediate the risk of recurrence may add new knowledge about novel strategies to modify such risk.

### Guidelines

In the last years, new treatment guidelines or updates have been published reporting consensus, insights and indications for the best management of BD, which is greatly justified by recent developments in treatment.

Many of these clinical recommendations are however not consistent. Some recommend treatment with MS or SGA monotherapy as first-choice, with aripiprazole and ziprasidone suggested in bipolar mania, as these SGAs show strong efficacy without significant tolerability issues<sup>35 60</sup>. Other guidelines recommend MSs and SGAs in association, particularly in the case of severe episodes<sup>52 61</sup>.

NICE<sup>7</sup>, usually recognized as producing gold standard guidelines, recommend lithium, valproate or olanzapine, with a recommendation to prescribe more than one of these medications if mood stabilization is poor.

Yet other guidelines<sup>62</sup> recommend combination treatment as a possible first line choice that is not restricted to particularly severe mania. There are still no firm conclusions regarding pharmaco-economic cost-benefit outcomes in terms of quality of life and maintenance of remission<sup>63</sup>.

The paucity of controlled head-to-head trials, differences in personal experience and opinions and timely updates may account for variations in guidelines<sup>39</sup>. Nevertheless, they provide a useful framework that can be used in conjunction with other recognized sources of information for the application of clinical wisdom<sup>1</sup>. Moreover, a reference standard of care in medico-legal proceedings, and interpretation on the basis of the patient's clinical circumstances, comorbidities, characteristics and resources is still needed.

Both clinical studies and guidelines indicate that combination regimens have become standard care in the treatment of the majority of patients with BD<sup>60 62 64-66</sup>. Monotherapy can be first-line choice for mild to moderate mania, while polytherapy - SGAs + MSs - has been demonstrated to be more efficacious. In reality, less than 10% of acute mania patients receive monotherapy, and clinical routine appears to be based on polypharmacy<sup>67 68</sup>.

Interestingly, guidelines have incorporated the empirical use of SGAs that pre-empted the available scientific evidence. In fact, RCTs followed the first case reports suggesting that they can be used to effectively treatment mania<sup>69 70</sup>. It is likely that clinicians made inferences from trials of SGAs in psychosis and clinical experience of FGAs.

Although guidelines remain a point of reference, they however cannot replace clinical knowledge and wisdom. This knowledge derives from observation of patients who are far from the *ideal patient* found in placebo-controlled trials, i.e. difficult patients with intrinsic complexity and variability. Because guidelines cannot take into account highly variable presentations, they should be seen as not prescriptive, but rather as flexible tools. Future guidelines will have to consider different subpopulations of patients affected by BD that are currently not studied adequately, e.g. large, prospective trials in unselected populations to bridge the gap between research and clinical practice. Guidelines should be able to offer theoretical and methodologically solid systematization of scientific knowledge by integration of data from RCTs together with rational clinical practice and experience. In this way, evidence-based data can likely be improved by increasing the confidence that any given evidence-based treatment is also effective in real word settings<sup>71</sup>.

However, guidelines may also be useful to reduce the unnecessary variability of clinical practice, and to help clinicians avoid mistakes and the use of non-scientific options. Clinicians must integrate recommendations from guidelines with experience, common sense and respect for patients by merging concepts such as efficacy, safety and tolerability, as this constitutes the concept of effectiveness.

## Conclusions

Several combinations of MSs and MSs with SGAs appear to be safe and effective despite paucity of controlled data/open-label studies. Individual factors make the difference in the clinical decision-making by taking into account the best evidence available data and patient needs<sup>72</sup>. Polypharmacy, as well as polypsychotherapy, with the possibility of complex combination therapy, may be the best way to match the complexity and comorbidities of BD<sup>2 73</sup>. In clinical practice, this is generally the rule rather

than the exception. However, while some combinations are supported by clinical trials, the efficacy of many has not been demonstrated, and may even prove harmful.

As with any medication, careful consideration has to be made when any drugs are combined. Multiple medication can easily fall into irrational associations if issues such as pharmacodynamic redundancy and interactions, pharmacokinetic interactions and inadequate dosing are not considered<sup>77</sup>. Recommendations for efficacy, safety, experience, cost of combination treatments and keeping in mind "what association to avoid" may increase the clinicians trust in guideline directives<sup>75</sup>.

Clinical vigilance and monitoring of safety are relevant aspects of safe BD treatment<sup>76</sup>. As with any medication regimen, combination therapies require continuous assessment of risks and benefits in terms of drug interactions and additional side effects considering the duration of the drug administration<sup>77</sup>.

The aim of the clinician is to 'exploit' possible drug interactions of combination treatment that are otherwise complex, potentially dangerous and with a risk of decreased compliance<sup>78</sup>. The golded rule to minimize toxic risks is to add new medication to the current regimen in modest doses with a subsequent slow increase in dose, particularly in elderly patients. One exception might be aripiprazole for whom dosage titration is suggested as not necessary<sup>79</sup>.

As observed with several medical therapies, a rational use of multiple agents can even lead to a avoidance of side effects. The use of several agents in combination can achieve an adequate degree of therapeutic response using each agent at doses below their own therapeutic dose and combination, side-effect threshold. This strategy can be safer than increasing the dosage of a single drug in monotherapy, which carries the probability of higher effectiveness but with more side effects<sup>2</sup>. Some data suggest that combination treatments could slower development of tolerance with single agents<sup>80</sup>.

The choice of an agent should be, moreover, based on the current individual clinical and biological predictors. This is the case for the SGAs risk of metabolic syndrome, where a large percentage of patients with BD are overweight (about 50% of women and 67% of men) or at a high risk for obesity<sup>81</sup>. The use of relatively weight-neutral compounds in an effort to avoid exacerbate weight-related problems should be considered<sup>2 82</sup>. Effective antipsychotics with safer profiles for EPS and hyperprolactinaemia should be preferred<sup>21 72 80</sup>.

Taking all these considerations into account, the data suggests that there is long-term benefit in continuing SGAs adjunctive to a MS after the acute phase, in order to reduce the risk of recurrence of a further mood event. The available studies on adjunctive/combination therapies provide pragmatic, reliable guidance to clinicians on why, when

and how to utilize such a strategy in an overall therapeutic approach in management of BD. Multiple treatment options offer the clinician the possibility of administering medications in an individually optimized manner.

It is likely that a single ideal treatment for all bipolar patients does not exist because of its intrinsic heterogeneity<sup>83</sup>. The need of further studies with long follow-up times on the cost/benefits of the use of different classes of psychotropic medications, particularly in association, is therefore warranted. This is also the case of several complex medical conditions, such as rheumatoid arthritis, coronary artery disease, congestive heart failure and diabetes, which frequently do not respond adequately to single agents and require complex combination therapy. While Occam's razor drives toward parsimony in diagnosis, Hickam's dictum is its counterbalancing principle suggesting the usefulness of taking into account multiple categories of diagnosis. In the case of a complex disorder such as BD, this dictum can suggest the utility of drug combinations such as those of MSs and SGAs.

#### Conflict of interest

In the past 5 years, prof. Rossi has received funding for advisory board membership and sponsored lectures from: Astra Zeneca, Bristol-Meyers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer, Stroder. He is not shareholder in any of these corporations. Dr. Paolo Stratta did not receive fundings from corporations.

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