

The role of antipsychotics and mood stabilizers in the treatment of bipolar disorder

Il ruolo degli antipsicotici e degli stabilizzatori dell'umore nel trattamento del disturbo bipolare

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Summary

Objectives

To provide an update on the pharmacologic treatment options for bipolar disorder with a focus on the role of antipsychotics.

Methods

Selective review of efficacy and tolerability data of acute and maintenance treatments for bipolar mania and bipolar depression, as monotherapy and in combination, supplemented by a discussion of differences in psychopharmacological profiles of antipsychotics with relevance for clinical switching and dosing paradigms.

Results

In a recent meta-analysis, efficacy for mania compared to placebo was demonstrated for all studied antipsychotics, lithium and selected antiepileptic medications, such as carbamazepine and valproic acid. Conversely, lamotrigine and topiramate were not superior to placebo. The pooled effect sizes of the agents separating from placebo ranged from 0.23 (small) to 0.66 (moderate), with overlapping 95% confidence intervals, indicating no significant differences in their efficacy vs. placebo in this indirect comparison. In head to head trials, when pooling results from multiple studies, antipsychotics were associated with a somewhat faster speed of onset and/or modestly greater efficacy than antiepileptics or lithium. While a class effect for antidopaminergic agents, but not anticonvulsants was observed for the treatment of mania, no class effect for either medication group was apparent for bipolar depression, for which the most robust results were found with quetiapine and olanzapine-

fluoxetine. Combining antipsychotics with conventional mood stabilizers was associated with faster and more profound symptom improvement compared to conventional mood stabilizer monotherapy. Finally, all agents shown to be effective for mania as well as lamotrigine were more effective than placebo for preventing mood episodes, but agents differed regarding the strength of the effect for preventing mania or depression. In addition, treatments for bipolar disorder differed regarding their adverse effects, influencing overall effectiveness. Switching from a higher metabolic risk antipsychotic to one with lower metabolic risk was shown to substantially improve metabolic health, but pharmacologically informed switching can improve switch success by minimizing potential withdrawal and rebound phenomena.

Conclusions

There has been a paradigm shift, in that antipsychotics are not merely adjunctive treatments during an acute, psychotic mania episode, but data support the routine use of atypical antipsychotics for the acute treatment of mania and maintenance treatment of bipolar disorder. Combination treatments have the chance of improving outcomes. More data and agents are needed to effectively treat bipolar depression, and important methodological effects of dosing and changes in specific symptom domains need to be addressed in future trials.

Key words

Bipolar disorder • Mania • Depression • Antipsychotics • Antiepileptics • Lithium • Mood Stabilizers • Efficacy • Safety • Psychopharmacology • Switching

Riassunto

Obiettivi

Fornire un aggiornamento sulle opzioni di trattamento farmacologico per il disturbo bipolare, con particolare attenzione al ruolo degli antipsicotici.

Metodi

Rassegna selettiva sui dati di efficacia e tollerabilità dei trattamenti acuti e di mantenimento per la mania bipolare e la

depressione bipolare, in monoterapia ed in associazione, con discussione sulle differenze dei profili psicofarmacologici degli antipsicotici in rapporto ai paradigmi di switch e dosaggio.

Risultati

In una recente meta-analisi, l'efficacia nella mania a confronto con il placebo è stata dimostrata per tutti gli antipsicotici studiati, per il litio e per alcuni farmaci antiepilettici selezionati, quali carbamazepina ed acido valproico. Diversamente, la lamotrigina ed il topiramato non sono stati superiori al placebo.

Corrispondenza

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Gli *effect size* cumulativi dei farmaci che si differenziavano dal placebo andavano da 0,23 (piccolo) a 0,66 (moderato), con intervalli di confidenza del 95% sovrappoventesi, indicando un'assenza di differenze significative tra l'efficacia dei due farmaci vs. placebo in questo confronto indiretto. Nelle prove clinico sperimentali a confronto diretto, quando si cumulavano i risultati di studi multipli, gli antipsicotici si associavano ad un'azione più rapida e/o un'efficacia modestamente superiore di quella degli antiepilettici o del litio. Mentre è stato osservato un effetto di classe per gli agenti antidopaminergici, ma non per quelli anticonvulsivanti per il trattamento della mania, nessun effetto di classe per nessun gruppo di farmaci si evidenziava per la depressione bipolare, per la quale i risultati più consistenti sono stati trovati per la quetiapina e per l'associazione olanzapina-fluoxetina. L'associare antipsicotici con stabilizzanti convenzionali si associava con un miglioramento sintomatologico più rapido e più intenso rispetto alla monoterapia con stabilizzanti convenzionali. Infine, tutti i farmaci che sono stati trovati efficaci per la mania ed anche la lamotrigina erano più efficaci del placebo nel prevenire gli episodi umorali, ma i vari farmaci differivano riguardo alla potenza del loro effetto preventivo sulla mania o sulla depressione. In aggiunta, i trattamenti del disturbo bipolare differivano per i loro effetti avversi e ciò influenzava la loro globale efficacia nel mondo reale. Cam-

Introduction

Bipolar disorder is a severe and often relapsing mental disorder that is characterized by abnormal mood and behaviors that often dramatically impair functioning. The separate or concurrent presentation of manic and depressive episodes and the not infrequent co-occurrence of psychotic symptoms all increase the complexity of this disorder¹. Moreover, some treatments might help one particular illness polarity (e.g., antidepressants: depression; typical antipsychotics: mania), but, at the same time, might worsen the other polarity. Furthermore, many, if not most, patients have comorbid psychiatric conditions, including anxiety disorders, obsessive compulsive disorder, attention deficit-hyperactivity disorder, impulsive and aggressive spectrum disorders and substance use disorders², as well as physical comorbidities, such as obesity and metabolic syndrome^{3,4}. In addition, subsyndromal, subthreshold and residual symptoms are not infrequent, which are associated with ongoing suffering, decreased functionality and an increased risk for future relapse. Therefore, a broad base of effective treatments is desirable that clinicians can choose from in order to tailor treatments to the patients' individual illness phase, polarity, treatment history and preferences. Furthermore, combined treatments are frequently used in clinical practice to navigate the complexities of bipolar disorder, and data informing these strategies are important. Finally, treatments need to be sustainable over time by balancing efficacy and tolerability as much as possible. Since switching among medications is quite common aiming

biare da un antipsicotico a rischio metabolico più alto ad uno a rischio metabolico più basso si associava ad un miglioramento importante della salute metabolica, ma tale cambio va basato su considerazioni farmacologiche per migliorare il successo del passaggio da un farmaco all'altro attraverso la minimizzazione dei potenziali fenomeni di astinenza e di rebound.

Conclusioni

Vi è stato uno spostamento paradigmatico, nel senso che gli antipsicotici non sono trattamenti meramente aggiuntivi durante un episodio acuto di mania con sintomi psicotici, ma i dati supportano l'uso routinario degli antipsicotici atipici per il trattamento acuto della mania e per il trattamento di mantenimento del disturbo bipolare. I trattamenti d'associazione hanno un'aumentata probabilità di migliorare gli esiti. Sono necessari più dati e farmaci per trattare efficacemente la depressione bipolare, mentre gli importanti effetti metodologici del dosaggio e modificazioni in specifici domini sintomatologici vanno affrontati in prove clinico sperimentali future.

Parole chiave

Disturbo bipolare • Mania • Depressione • Antipsicotici • Antiepilettici • Litio • Stabilizzatori dell'umore • Efficacia • Sicurezza • Psicofarmacologia • Switching

to improve one or both aspects of the often delicate risk-benefit profile of long-term treatment, pharmacologically based and informed switching can be used to enhance the outcomes of patients with bipolar disorder⁵.

Material and methods

This is a selective review of the more recent evidence regarding the efficacy and tolerability of antipsychotics in bipolar I disorder. Results from recent meta-analyses and selected individual studies are presented and the evidence for the utility of antipsychotics in the treatment of acute mania, bipolar depression and relapse prevention is reviewed. Data from studies with lithium and anticonvulsants (also known as conventional mood stabilizers) are presented to provide direct or indirect comparative context. Moreover, pharmacologic profiles of antipsychotics with clinical relevance for antipsychotic dosing and switching will be reviewed.

Results

Antimanic efficacy

A recent meta-analysis examined results from 38 randomized, placebo-controlled short-term studies that included 10,800 patients with pure or mixed bipolar I mania and reported on 56 drug-placebo comparisons of 17 agents⁶. Of the tested agents, 13 (76%) were more effective than placebo. Their pooled effect size for mania improvement (Hedges' *g* in 48 trials) was 0.42 [confidence interval (CI): 0.36-0.48]; pooled responder risk ratio (46 trials) was

1.52 (CI: 1.42-1.62); responder rate difference (RD) was 17% (drug: 48%, placebo: 31%), yielding an estimated number-needed-to-treat of 6 (all $p < 0.0001$). However, while superiority to placebo was found with all examined antipsychotics (aripiprazole, asenapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) and lithium, several anticonvulsants, such as topiramate and lamotrigine, were not superior to placebo⁶. The pooled effect sizes of the agents that separated from placebo ranged from 0.23 (small) to 0.66 (moderate). Moreover, all 95% confidence intervals for the effect sizes of the agents that separated from placebo overlapped, indicating no significant differences in the efficacy of atypical antipsychotics, haloperidol, lithium, valproate and carbamazepine vs. placebo in this indirect comparison⁶. These findings indicate that for mania, dopamine blocking agents have a class effect, while among antiepileptic medications, which interact with ion channels and second messenger systems, there is no antimanic class effect. The authors concluded that these data support the efficacy of most clinically used antimanic treatments, but encouraged more head-to-head studies and the development of agents with even greater efficacy⁶.

Since different classes of medications with different mechanisms have been found effective for the treatment of mania, two questions arise: first, are there differences in efficacy between antipsychotics and lithium or anticonvulsants, such as valproate or carbamazepine? Second, is a combination of any of these three different medication types associated with greater efficacy than monotherapy?

First, in head to head comparisons, antipsychotics seemed to either be associated with a somewhat faster speed of onset and/or lead to mildly greater efficacy than antiepileptics or lithium, at least when pooling multiple trials together and with lower than optimal mean serum levels of lithium and valproate⁶. Moreover, at least in short-term trials, there was no difference in the degree of superiority of second-generation antipsychotics or first-generation antipsychotics when studied against placebo⁶. For the acute treatment, short acting injectable antipsychotics indicated for bipolar mania⁷ provide an additional treatment option for rapid symptom control. Second, when examining studies that assessed the efficacy of combination treatments, studies have overwhelmingly shown that combining two effective antimanic agents from different classes results in a faster speed of onset of efficacy and greater symptom reduction as well as greater response and remission rates compared with monotherapy. This has been shown for aripiprazole, haloperidol, olanzapine, quetiapine and risperidone when added on to lithium or valproic acid compared to lithium or valproic acid monotherapy^{8,9}. In

short term trials, no separation from placebo was seen with the addition of ziprasidone⁸ or of gabapentin¹⁰ to lithium or valproate.

Efficacy for bipolar depression

While antidepressants have long been used in clinical practice for the treatment of bipolar depression, randomized controlled evidence for their safety and efficacy is slim.

Concerns have been raised about the potential of antidepressants for increasing the risk of mixed mania presentations, manic switches, rapid cycling and "roughening" of the illness course¹¹. Moreover, studies also do not support significant advantages when adding an antidepressant to ongoing mood stabilizer treatment regarding the time to or rate of response, remission and durable remission^{12,13}.

A recent meta-analysis of 19 placebo controlled trials investigated the effectiveness of treatments of bipolar depression¹⁴. Medications included several second-generation antipsychotics, lithium, antiepileptics, phenelzine and paroxetine. Most studies were identified for quetiapine (5 trials) and lamotrigine (6 trials). Only selected agents showed superior efficacy for bipolar depression compared to placebo.

The greatest reductions in Montgomery-Asberg Depression Rating Scale (MADRS) total scores vs. placebo were reported for the olanzapine-fluoxetine combination (1 trial: -6.6; 95% CI, -9.59 to -3.61; $p = 0.000$) and quetiapine monotherapy (5 trials: for 300 mg/d, -4.8; 95% CI, -6.18 to -3.49; $p = 0.000$; for 600 mg/d, -4.8; 95% CI, -6.22 to -3.28; $p = 0.000$), with quetiapine monotherapy also showing the highest reduction in HAM-D scores (4 trials: -4.0; 95% CI, -5.0 to -2.9; $p = 0.000$).

Moreover, compared to placebo, quetiapine, olanzapine-fluoxetine, olanzapine, lamotrigine, valproate and imipramine showed significantly greater rates of response, and quetiapine, olanzapine-fluoxetine, olanzapine showed greater rates of remission¹⁴. In 2 fixed dose trials comparing ziprasidone with placebo in bipolar depressed patients, which had not been included in the aforementioned meta-analysis, ziprasidone also failed to separate from placebo¹⁵.

However, when interpreting these results, it is important to consider differences in the methodology across the studies as well as the differential impact of medications on specific symptom domains. The latter point is relevant, as efficacy is measured by assessing change in a total score of a rating scale that pools together a diverse range of symptoms.

For example, in a trial comparing olanzapine, olanzapine-fluoxetine and placebo in patients with bipolar depression, both active treatments separated significantly

from placebo on the MADRS total score as early as week one, with numerical superiority of the olanzapine-fluoxetine combination¹⁶. However, when examining the effect on individual MADRS items, olanzapine monotherapy separated only from placebo regarding the reversal of neurovegetative signs, showing significant improvement of decreased sleep and appetite, as well as of psychomotor restlessness. By contrast, olanzapine-fluoxetine combination also separated in terms of core depressive symptoms, including reported and apparent sadness, inability to feel, and pessimistic thoughts. This raises the possibility that agents not possessing relevant sedating properties, such as lamotrigine and ziprasidone, might have a disadvantage when assessing total scores only¹⁷.

Maintenance treatment and relapse prevention

The maintenance phase in any chronic disorder is arguably the most important and extensive treatment period. Of note, different from schizophrenia where structural brain abnormalities are apparent at the time of the first episode, brain structural deficits seem to emerge after successive manic episodes¹⁸, even though a substantial number of patients had syndromal depressive episodes preceding the first episode of mania. Moreover, a greater number of total mood episodes predicted the likelihood of and shorter time to relapse, with more consistent and stronger effects regarding relapse to a mania episode than to a depressive episode¹⁹. Interestingly, the same moderating effect of prior mood episodes was not observed in a meta-analysis of psychological treatments specifically designed for preventing or delaying relapses in bipolar disorders²⁰. Nevertheless, taken together, these data underscore the importance of preventing relapses that are more likely when patients still have residual symptomatology²¹, highlighting the need to optimize treatments with the clear aim of achieving euthymia.

A number of longer-term studies have established the utility of all studied atypical antipsychotics, including aripiprazole, olanzapine, quetiapine, and ziprasidone for relapse prevention, either in monotherapy²²⁻²⁴ or in combination with lithium or valproic acid²⁵⁻²⁹. Among conventional mood stabilizers, lithium and lamotrigine also established maintenance treatment³⁰⁻³¹. Moreover, the recent 2-year effectiveness trial by the BALANCE group that compared lithium and valproate monotherapy with a combination of lithium and valproate in bipolar disorder patients who had tolerated 8 weeks of lead in treatment with lithium plus valproate indicated that both the combination treatment and lithium monotherapy were superior to valproate monotherapy in preventing the next mood episode³².

Despite these encouraging data, most treatments do not prevent a manic and depressive episode equally well. Although results are influenced by the mood polarity of the last episode, which is a strong predictor of the subsequent mood polarity, currently only quetiapine seems to be equally potent in preventing a next manic or depressive episode³³. Most agents prevent manic episodes better, with the exception of lamotrigine, which more potently prevents depressive episodes³³.

Tolerability

Tolerability profiles have an impact on the acceptability of treatments, subjective well-being, physical health outcomes and adherence. Relevant adverse effects of medications used for bipolar disorder, Black Box warnings and monitoring suggestions are listed in Table I.

Although side effects remain a concern with all mood stabilizers and antipsychotics, the focus has shifted in recent years from gastrointestinal and neuromotor side effects to cardiovascular and metabolic risk factors, including weight gain, obesity, dyslipidemia, insulin resistance, diabetes and coronary artery disease³⁴⁻³⁵. At least during antipsychotic monotherapy and in patients who received prior antipsychotic treatment, olanzapine and clozapine have been associated with the largest weight gain, risperidone and quetiapine appear to be associated with intermediate weight gain, and aripiprazole and ziprasidone have the least weight gain potential³⁶⁻³⁷. Although risperidone and quetiapine seem to have a similar weight gain potential, quetiapine appears to be associated with a greater liability to cause metabolic abnormalities, especially regarding lipid metabolism²⁶⁻²⁷. Moreover, there is some suggestion that first episode and antipsychotic-naïve patients are at highest risk for antipsychotic-induced weight gain and metabolic side effects and that none of the antipsychotics is entirely weight neutral³⁸.

Clinically relevant endocrine side effects include lithium-related hypothyroidism³⁹ and valproate-related polycystic ovary-like symptoms in females of childbearing age⁴⁰. Prolactin elevation varies considerably across antipsychotics, with risperidone and paliperidone causing even greater increases than haloperidol, ziprasidone and olanzapine having a low intermediate risk, and quetiapine and clozapine causing no appreciable increase in prolactin⁴¹. Aripiprazole, due to its partial D2 agonism, generally causes some decrease in prolactin. Although sexual dysfunction does not directly follow prolactin changes or endpoint values, the general liability of antipsychotics to cause sexual functioning abnormalities is associated with the potential to increase prolactin levels⁴¹.

While extrapyramidal symptoms (EPS)⁴² and tardive dyskinesia³⁵ are generally of less concern with second-gen-

TABLE I.
Side Effects, Black Box Warnings, and Monitoring Recommendations of Medications with FDA Indication for Bipolar Disorder.
Effetti collaterali, avvertenze e raccomandazioni sul monitoraggio con indicazione della Food and Drug Administration per il disturbo bipolare.

Medication	Common Adverse Effects	Black Box Warnings	Monitoring Recommendations
<i>Mood stabilizers</i>			
Carbamazepine	Dizziness, drowsiness, unsteadiness, nausea, and vomiting, lowering of its own blood level and of other hepatically metabolized medication levels	Serious and potentially fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome; aplastic anaemia and agranulocytosis	Signs and symptoms of hepatic, hematologic, or dermatologic side effects; CBCs, platelet measurements, during the first 2 months, liver function tests every 2 weeks; thereafter, blood counts and liver function tests at least every 3 months, with more frequent monitoring in patients with signs of hematologic or hepatic abnormalities
Divalproex/valproic acid	Gastrointestinal symptoms (nausea, vomiting, heartburn); less frequently, dermatologic effects (rash, alopecia) and neurologic effects (drowsiness, irritability, ataxia), low platelet count, hair loss	Hepatotoxicity, teratogenicity, pancreatitis	PCOS may develop with VPA treatment, for stable patients taking VPA, hematologic and hepatic function at least every 6 months; patients who are unable to reliably report signs and symptoms of VPA toxicity should be monitored more frequently
Lamotrigine	Dizziness, ataxia, somnolence, headache, double-vision, blurred vision, nausea, rash	Life-threatening serious rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death; additional factors that may increase risk of rash may include: coadministration with valproate and exceeding recommended initial dose or dose escalation of lamotrigine	Instruction to patient and family to report each rash and routine inquiry about this
Lithium	Fine hand tremor, mild thirst, polyuria, nausea; early signs of lithium intoxication include diarrhea, vomiting, drowsiness, muscular weakness, dysarthria and lack of coordination	Lithium toxicity	Before starting lithium, general medical history, physical exam, BUN, creatinine level, pregnancy test, thyroid function. For patients > age 40, ECG with rhythm strip, CBC, monitor for neurologic toxicity
<i>Antipsychotics</i>			
Aripiprazole	Nausea, vomiting, light-headedness, somnolence, constipation, postural dizziness, restlessness, akathisia	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs; increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders	Weight, BMI, and healthy lifestyle routinely; fasting glucose and lipids and blood pressure at baseline, 3 months, 12 months and annually; EPS and abnormal involuntary movements at baseline, during titration and 3-monthly thereafter
Asenapine	Somnolence, dizziness, EPS symptoms other than akathisia, weight gain	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs	As for aripiprazole

(continues)

Table 1 – continued.

Medication	Common Adverse Effects	Black Box Warnings	Monitoring Recommendations
<i>Mood stabilizers</i>			
Chlorpromazine	Drowsiness, postural hypotension, EPS	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs	As for aripiprazole plus frequent CBC during first few months of treatment for patients with pre-existing low WBC count or a history of drug-induced leukopenia/neutropenia
Olanzapine	Dry mouth, edema, postural hypotension, weight gain, elevated plasma glucose and triglycerides	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs	As for aripiprazole
Olanzapine-fluoxetine combination	Disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, blurred vision, weight gain	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs; increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders	As for aripiprazole
Quetiapine	Dry mouth, sedation, dizziness, somnolence, postural hypotension, weight gain	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs; increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders	As for aripiprazole plus initial lens examination (for cataracts, based on animal data only) when starting treatment and every 6 months thereafter
Risperidone	EPS at high doses, weight gain, tachycardia, hyperprolactinemia, headache, dizziness, abdominal pain	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs	As for aripiprazole
Ziprasidone	Somnolence, EPS including akathisia, dizziness, abnormal vision, asthenia, vomiting	Increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs	As for aripiprazole plus baseline serum potassium and magnesium measurements for patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances; patients with low serum potassium and/or magnesium should be repeated prior to treatment to avoid ECG/cardiac conduction abnormalities
BUN: blood urea nitrogen; ECG: electrocardiogram; EPS: extrapyramidal symptoms; MDD: major depressive disorder; PCOS: polycystic ovary syndrome.			

eration antipsychotics than with older agents, there has been a suggestion that mood disorder patients might be at increased risk for neuromotor adverse effects. Therefore, clinicians should assess motor function at baseline and monitor motor side effects during antipsychotic dose titration and at 3-month intervals after reaching the target

dose. The same is true for akathisia that is more likely with aripiprazole than with other second-generation antipsychotics, but still much less likely than with typical antipsychotics⁴³. Moreover, most akathisia events with aripiprazole occurred early, were short lived and did not lead to treatment discontinuation⁴³.

Practical psychopharmacology

At least some degree of clinical effects can be predicted from the pharmacodynamic receptor binding profile of antipsychotics. Pharmacokinetic differences in antipsychotic half lives also impact on clinical effects. Figure 1 summarizes the relative binding affinities of selected antipsychotics for some of the clinically most relevant known neurotransmitter receptors⁵. The numerical values denote the concentration of a medication required to occupy 50% of a given receptor type (i.e., lower number equals stronger binding). In Figure 1, all binding profile values are set relative to the concentration required to occupy 50% of dopamine D2 receptors, which was set as the value 1. This visual display helps to identify, which receptors are blocked more potently than dopamine (i.e., receptor blockade will have clinically relevant effects) and which receptors are blocked less potently than dopamine less potently than dopamine (i.e., blockade will be less pronounced or have little to no clinically relevant effects). As seen in Figure 1, the individual antipsychotics differ substantially regarding the binding to non-dopaminergic receptors relative to the binding that is thought to be closely

related to antimanic, anti-aggressive and antipsychotic efficacy (i.e., approximately 60%-80% D2 binding)⁵. The differences in the relative binding potential achieve particular relevance when considering switching strategies. Antipsychotic switching is relatively common and may be considered in non-refractory patients who only responded partially or not at all to the current treatment (i.e., residual symptoms that cause distress or impair functioning), or when side effects are sufficiently severe or impairing. However, switching can also be associated with destabilization, which may be related to withdrawal or rebound effects⁵. These rebound effects can make it difficult to interpret the efficacy of the new agent since insufficient efficacy can be due to either discontinuation-related exacerbations or continuation/exacerbation of illness related symptoms. Moreover, switching outcomes are further complicated if the new antipsychotics is dosed insufficiently, so that the net dopamine blockade is insufficient. To avoid rebound symptoms, it is important to utilize switching practices that take into account differences in pharmacodynamic profiles (Fig. 1). For example, a slower, overlapping switch should be considered to avoid rebound

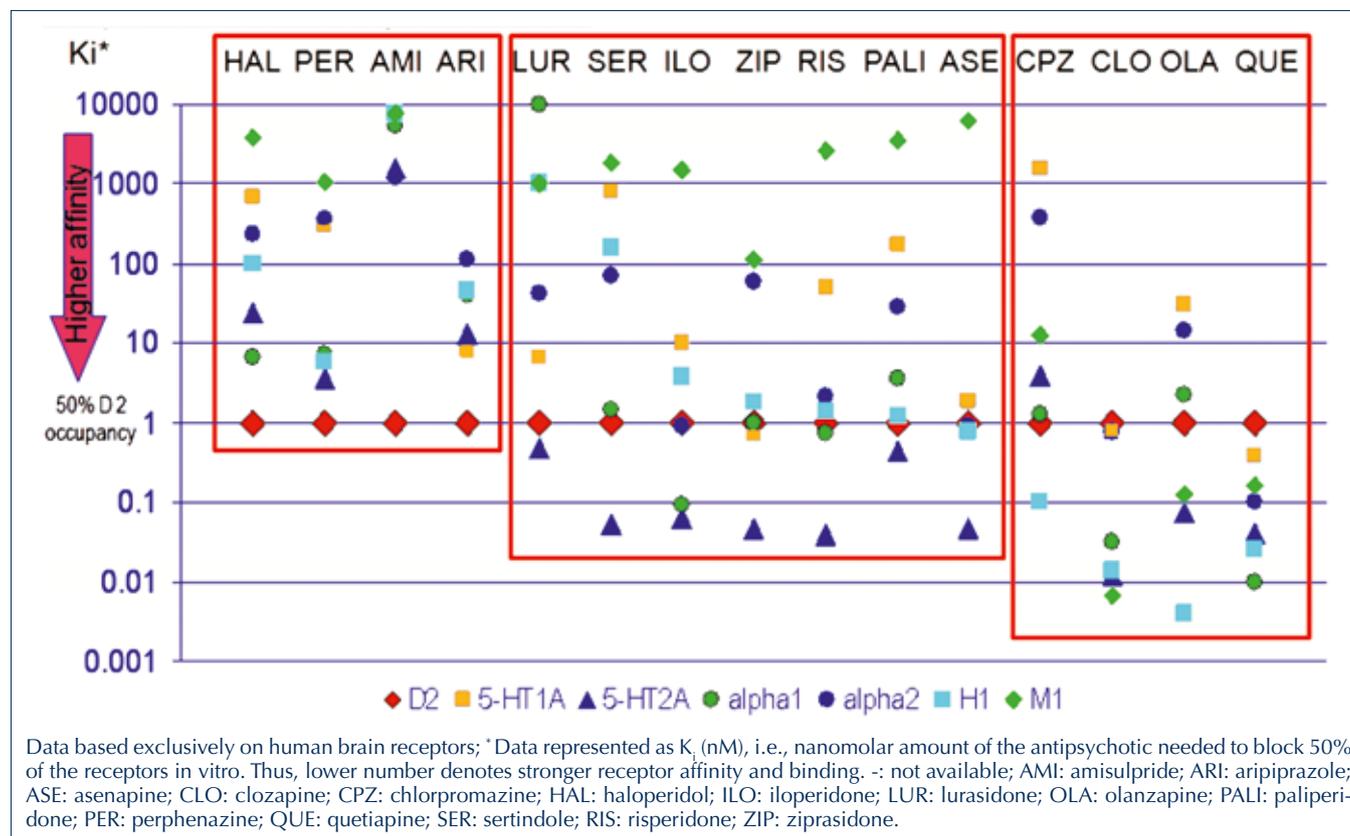


FIGURE 1. Approximate Relative Receptor Binding Affinities of Selected Antipsychotics (based on Correll, 2010⁵; PI for Asenapine and Lurasidone and Brian Roth NIH Psychoactive Drug Screening Program (<http://pdsp.med.unc.edu>)). *Affinità di legame recettoriale relative approssimative di antipsicotici selezionati (basato su Correll, 2010⁵; PI for Asenapine and Lurasidone and Brian Roth NIH Psychoactive Drug Screening Program (<http://pdsp.med.unc.edu>)).*

side effect phenomena (e.g., rebound anxiety, insomnia, or agitation) from histaminergic or cholinergic blockade (Table II)⁵. Similarly a slow, overlapping plateau switch might be necessary when switching from a high(er)-affinity dopamine receptor antagonist to quetiapine or clozapine, which have less affinity for the receptor, or to a partial agonist, such as aripiprazole, in order to avoid dopamine rebound phenomena that can result from insufficient D₂ blockade during the switch. Dopamine rebound can manifest as transient intra-switch restlessness or worsening of psychosis, mania, or agitation, and should be monitored and possibly be treated by increasing the dose of the post-switch antipsychotic or by adding sedating medications until the switch has been completed⁵. In addition to pharmacodynamic rebound and withdraw-

al symptoms, differences in the half-life of the pre- and post-switch antipsychotic or in the absorption can result in pharmacokinetic rebound phenomena. The risk for rebound phenomena is particularly high when the switch is abrupt and when switching from a shorter half life antipsychotic to one with a longer half life.

To minimize the risk of rebound phenomena or when a quick switch is intended or desirable, one can either employ a plateau cross-titration (Fig. 2) or use targeted dose adjustment and/or (time limited) comedications strategies (Table III)⁵.

Discussion

The treatment of bipolar disorder is arguably one of the most complex tasks in the management of mentally ill

TABLE II.

Potential Rebound Effects Due to Withdrawal from Specific Receptors After Compensatory Upregulation and Switch to an Agent with Substantially Lower Blockade at these Receptors. *Potenziali effetti di rebound dovuti a sospensione dopo up-regulation recettoriale compensatoria e passaggio ad un farmaco con minore affinità per questi recettori.*

Receptor	Blockade	Rebound/Withdrawal
D ₂	Antipsychotic, antimanic, antiaggressive, EPS/akathisia, tardive dyskinesia, increased prolactin	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
H ₁	Anxiolytic, sedation, weight gain, anti-EPS/akathisia	Anxiety, agitation, insomnia, EPS/akathisia
M ₁ (central)	Memory, cognition, dry mouth, anti-EPS/akathisia	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia
M ₂₋₄ (peripheral)	Blurry vision, constipation, urinary retention, tachycardia, hypertension	Diarrhea, diaphoresis, nausea, vomiting, bradycardia, hypotension, syncope
5-HT _{2A}	Anti-EPS/akathisia, ?antipsychotic	EPS/akathisia, ?psychosis

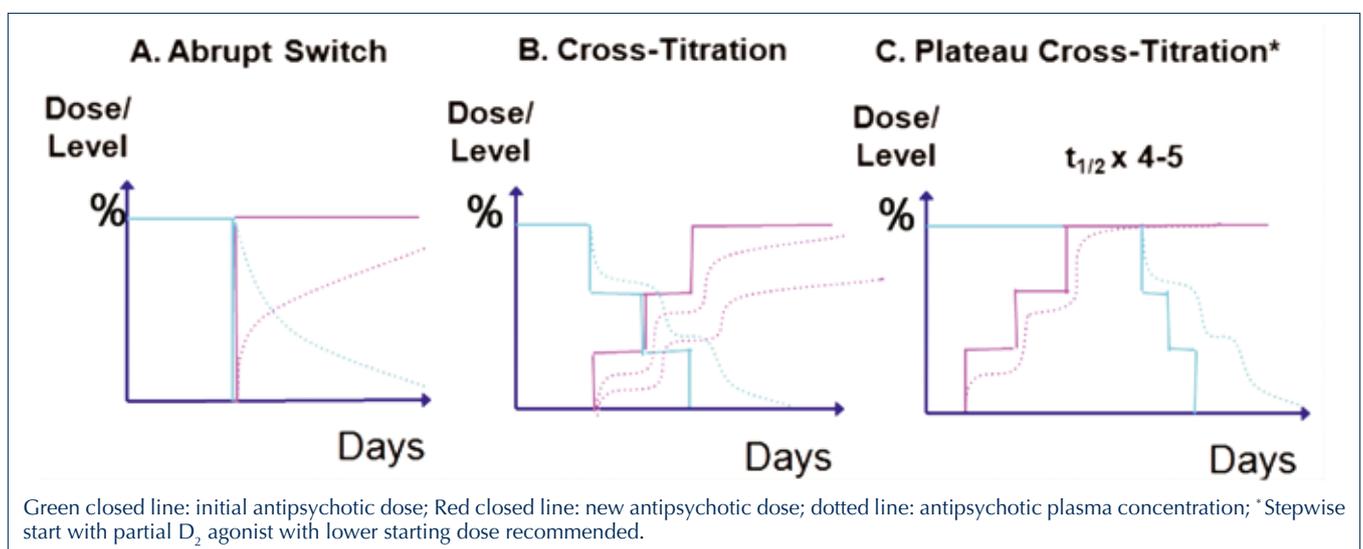


FIGURE 2.

Different Switch Techniques Among Antipsychotics (adapted from Correll, 2006)⁴⁴. *Varie tecniche di passaggio da un farmaco all'altro tra antipsicotici (adattato da Correll, 2006)⁴⁴.*

TABLE III.

Targeted Adjuvant Treatment Options Aimed at Minimizing Pharmacodynamic and Pharmacokinetic Rebound and Withdrawal Effects During Antipsychotic Switching. *Opzioni di trattamento aggiuntivo mirato avente lo scopo di minimizzare gli effetti farmacodinamici e farmacocinetici di rimbalzo e di astinenza durante il passaggio da un antipsicotico ad un altro.*

Side effect	Corrective approach or (transient) adjuvant medications
Akathisia	Lower dose or partial agonist, slow down switch Add benzodiazepine, antihistamine, beta-blocker, gabapentin
Mania, psychosis	Slow/reverse down titration of prior antipsychotic, increase new antipsychotic; add benzodiazepine, valproate
Agitation	Less likely with lower starting dose, slow switch, increase new antipsychotic; add benzodiazepines, valproate
Anxiety	Use lower starting dose, slow switch, restrict excessive caffeine use Add benzodiazepine, antihistamine, gabapentin
Insomnia	Less likely with lower starting dose, slow switch, restrict excessive caffeine use, add benzodiazepine, hypnotic, antihistamine
Nausea/vomiting	Less likely with lower starting dose, slow switch Consider dosing twice daily, give with fatty food (to slow absorption) Add antihistamines or anti-emetics if needed

patients. It consists of treatment considerations regarding the management of acute mania and its opposite pole, acute depression, as well of maintenance treatment and relapse prevention into either manic or depressive episodes. In addition, the treatment is complicated by the fact that depression and mania can coincide in the form of mixed mania, that patients might have psychotic symptoms or a rapid cycling subtype bipolar disorder and that suicidality and completed suicide are unfortunately not infrequent.

Lithium and antiepileptic medications have been the mainstay of treatment of bipolar disorder. Over the last decade, however, trials in bipolar disorder have confirmed that atypical antipsychotic monotherapy is superior to placebo and, at least, as effective as conventional mood stabilizers in the treatment of acute mania^{6,30,45,46}. More Effective treatments exist for the manic phase and psychotic symptoms, as well as for the prevention of manic or mixed relapse, while the treatment armamentarium is more limited regarding the treatment of acute bipolar depression and of the prevention of recurring bipolar depression^{14,33}.

Moreover, most studied antipsychotics are efficacious for acute mania^{8,9} and for relapse prevention²⁵⁻²⁹ when added to lithium or valproate for patients showing no or a partial response to lithium or valproate alone. However, conventional 2-arm study designs could benefit from a third antipsychotic monotherapy arm, and antipsychotic monotherapy should also be tested against a combination of lithium and valproate. Moreover, except for quetiapine and lamotrigine all other agents are less effective for the prevention of bipolar depression³³.

Furthermore, differences in adverse event profiles among available treatment options for bipolar disorder affect treatment effectiveness, a measure that incorpo-

rates the risk-benefit balance, tolerability, acceptability and patient satisfaction, adherence and quality of life. Among the adverse effects with greatest importance for longevity are adverse cardiovascular effects³⁸. While causal pathways for these adverse outcomes are complex, and strategies to improve health and wellness are needed, multiple lines of evidence suggest that behavioral, environmental, and treatment variables together significantly contribute to poor health outcomes in bipolar disorder³⁸. Because mental health and physical health are intricately related, both must be addressed to achieve full recovery.

Based on these considerations, recent treatment guidelines have subdivided level A evidence treatments (i.e., evidence based superiority against placebo and/or non-inferiority against a standard treatment) into first line and second line agents. Given roughly similar efficacy signals of effective treatment options, these recommendations are based on risk-benefit considerations⁴⁷.

Switching of treatments due to (partial) inefficacy is not uncommon. Moreover, switching from a higher metabolic risk antipsychotic to one with lower metabolic risk can substantially improve metabolic health. In order to maintain or achieve sustained mental health during an antipsychotic switch, pharmacodynamic and pharmacokinetic properties of the previous and the new antipsychotic need to be considered to avoid relevant withdrawal and rebound phenomena during switching. Finally, to maintain or improve physical health, regular cardiometabolic monitoring needs to be conducted and strategies should focus on early education and prevention through simple lifestyle guidance and the use of lower-risk treatments as first line strategies whenever possible.

Conclusions

The treatment of bipolar disorder is arguably one of the most complex tasks in the management of mentally ill patients. Various effective treatment options exist for the manic phase and psychotic symptoms, as well as for the prevention of manic or mixed relapse, while the treatment armamentarium is more limited regarding the treatment of acute bipolar depression and of the prevention of recurring bipolar depression.

Recent data atypical antipsychotic treatment trials in bipolar disorder have confirmed that atypical antipsychotic monotherapy is superior to placebo regarding an acute manic and mixed episodes. Moreover, agents that are effective antimanic agents, as well as lamotrigine prevent recurrence of mood episodes, while the treatment and prevention of bipolar depression remains an area of need. Furthermore, combining antipsychotics with conventional mood stabilizer treatment is superior to mood stabilizer monotherapy. These data provide the basis for a paradigm shift, in that antipsychotics are not merely adjunctive treatments during an acute psychotic mania episode, but atypical antipsychotics have become an integral part of routine treatment for the acute and maintenance treatment of bipolar disorder. However, the availability of a number of effective agents, increase the importance of choosing and combining agents with the most beneficial risk:benefit ratio and greatest individualized patient acceptability. Residual symptoms, comorbidities, side effects, and nonadherence can interfere with treatment success. Therefore, measurement-based monitoring of beneficial and adverse effects and an increased focus on targeting both psychiatric and physical health via multimodal individualized treatment has the greatest chance of maximizing treatment outcomes in patients with bipolar disorder.

Conflict of interest

Prof. C.U. Correll has been a consultant for, received grant/research support and honoraria from and been on the speakers/advisory boards of Actelion, AstraZeneca, Biotis, Bristol-Myers Squibb, Cephalon, Eli Lilly, IntraCellular Therapies, Ortho-McNeill/Janssen/J&J, Merck, Novartis, Otsuka, Pfizer, and Sepracor/Sunovion, the Feinstein Institute for Medical Research, the National Institute of Mental Health (NIMH), and the National Alliance for Research in Schizophrenia and Depression (NARSAD).

References

- 1 Goodwin G, Fleischacker W, Arango C, et al. *Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice*. Eur Neuropsychopharmacol 2009;19:520-32.
- 2 Merikangas KR, Jin R, He JP, et al. *Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative*. Arch Gen Psychiatry 2011;68:241-51.
- 3 Fagiolini A, Frank E, Scott JA, et al. *Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians*. Bipolar Disord 2005;7:424-30.
- 4 Correll CU, Druss BG, Lombardo I, et al. *Findings of a U.S. national cardiometabolic screening program among 10,084 psychiatric outpatients*. Psychiatr Serv 2010;61:892-8.
- 5 Correll CU. *From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics*. Eur Psychiatry 2010;25(Suppl 2):S12-21.
- 6 Yildiz A, Vieta E, Leucht S, et al. *Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials*. Neuropsychopharmacology 2011;36:375-89.
- 7 Zimbroff DL, Marcus RN, Manos G, et al. *Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole*. J Clin Psychopharmacol 2007;27:171-6.
- 8 Perlis RH, Welge JA, Vornik LA, et al. *Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials*. J Clin Psychiatry 2006;67:509-16.
- 9 Vieta E, T'joen C, McQuade RD, 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;165:1316-25.
- 10 Pande AC, Crockatt JG, Janney CA, et al. *Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy*. Gabapentin Bipolar Disorder Study Group. Bipolar Disord 2000;2:249-55.
- 11 Berk M, Ng F, Dodd S, et al. *Do we need to flick the switch? The need for a broader conceptualization of iatrogenic course aggravation in clinical trials of bipolar disorder*. Psychiatry Clin Neurosci 2010;64:367-71.
- 12 Sachs GS, Nierenberg AA, Calabrese JR. *Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. Effectiveness of adjunctive antidepressant treatment for bipolar depression*. N Engl J Med 2007;356:1711-22.
- 13 Sachs GS, Dupuy JM, Wittmann CW. *The pharmacologic treatment of bipolar disorder*. J Clin Psychiatry 2011;72:704-15.
- 14 Vieta E, Locklear J, Günther O, et al. *Treatment options for bipolar depression: a systematic review of randomized, controlled trials*. J Clin Psychopharmacol 2010;30:579-90.
- 15 Sachs GS, Ice KS, Chappell PB, et al. *Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: a randomized, double-blind, placebo-controlled trial*. J Clin Psychiatry 2011 May 3 [Epub ahead of print].
- 16 Tohen M, Vieta E, Calabrese J, et al. *Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression*. Arch Gen Psychiatry 2003;60:1079-88.
- 17 Thase ME, Jonas A, Khan A, et al. *Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies*. J Clin Psychopharmacol 2008;28:13-20.
- 18 Strakowski SM, DelBello MP, Zimmerman ME, et al. *Ventricular and periventricular structural volumes in first-*

- sus multiple-episode bipolar disorder. *Am J Psychiatry* 2002;159:1841-7.
- 19 Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord* 2011;13:87-98.
- 20 Lam DH, Burbeck R, Wright K, et al. Psychological therapies in bipolar disorder: the effect of illness history on relapse prevention - a systematic review. *Bipolar Disord* 2009;11:474-82.
- 21 Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2006;163:217-24.
- 22 Keck PE Jr, Calabrese JR, McIntyre RS, et al.; Aripiprazole Study Group. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry* 2007;68:1480-91.
- 23 Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 2010;71:150-62.
- 24 McElroy SL, Weisler RH, Chang W, et al.; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 2010;71:163-74.
- 25 Tohen M, Chengappa KN, Suppes T, 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.
- 26 Suppes T, Vieta E, Liu S, et al; Trial 127 Investigators. 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;166:476-88.
- 27 Vieta E, Suppes T, Eggens I, et al. 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;109:251-63.
- 28 Bowden CL, Vieta E, Ice KS, et al. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010;71:130-7.
- 29 Marcus R, Khan A, Rollin L, 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;13:133-44.
- 30 Smith LA, Cornelius V, Warnock A, et al. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007;9:394-412.
- 31 Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* 2004;65:432-41.
- 32 BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 2010;375:385-95.
- 33 Malhi GS, Adams D, Cahill CM, et al. The management of individuals with bipolar disorder: a review of the evidence and its integration into clinical practice. *Drugs* 2009;69:2063-101.
- 34 Correll CU. Balancing efficacy and safety in the treatment with antipsychotics. *CNS Spectrums* 2007;12(Suppl 17):12-20, 35.
- 35 Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry* 2008;21:151-6.
- 36 Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005;19(Suppl 1):1-93.
- 37 Parsons B, Allison DB, Loebel A, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res* 2009;110:103-10.
- 38 Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med* 2011;17:97-107.
- 39 Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. *Clin Pract Epidemiol Ment Health* 2006;2:23.
- 40 Joffe H, Cohen LS, Suppes T, et al. Longitudinal follow-up of reproductive and metabolic features of valproate-associated polycystic ovarian syndrome features: A preliminary report. *Biol Psychiatry* 2006;60:1378-81.
- 41 Byerly M, Suppes T, Tran QV, et al. Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. *J Clin Psychopharmacol* 2007;27:639-61.
- 42 Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2010 May 31 [Epub ahead of print].
- 43 Kane JM, Barnes TR, Correll CU, et al. Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials. *J Psychopharmacol* 2010;24:1019-29.
- 44 Correll CU. Real-life switching strategies with second-generation antipsychotics. *J Clin Psychiatry* 2006;67:160-1.
- 45 Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. *Bipolar Disord* 2009;11(Suppl 2):45-54.
- 46 Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord* 2010;12:116-41.
- 47 Grunze H, Vieta E, Goodwin GM, 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;10:85-116.