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REVIEW

Antipsychotic switching in bipolar disorders: a systematic review

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Abstract

With the increasingly widespread use of antipsychotics in bipolar disorder (BD), switching among these agents and between antipsychotics and mood stabilizers has become more common, in particular, since the introduction of the novel atypical antipsychotics with mood stabilizer properties. This systematic review aims to provide a comprehensive update of the current literature in BD about the switching of antipsychotics, among them and between them and mood stabilizers, in acute and maintenance treatment. We conducted a comprehensive, computerized literature search using terms related to antipsychotic switching in BD in the PubMed/Medline, PsycINFO, CINAHL database; the Cochrane Library and; the Clinicaltrials.gov web up to January 9th, 2013 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The search returned 4160 articles. After excluding duplications, reviews, case reports and studies that did not fulfil the selection criteria, 8 studies were included. Not only have few articles on antipsychotic switching been published but also recruitment in most studies included mixed samples of patients. In general, antipsychotic switching, regardless of the route of drug administration, was well tolerated and no interference was shown in antipsychotic effectiveness during the interchange of drugs. Metabolic improvement was perceived when the switch involved antipsychotics with a low metabolic risk profile. The evidence-base for antipsychotic switching in BD is scant, and little controlled data is available. Switch from quetiapine to lithium and from risperidone to olanzapine has proven successful. Switching to antipsychotics with low metabolic risk had some positive impact on several safety measures. In stabilized patients, the plateau cross-taper switch may be preferred.

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Key words: Antipsychotics, bipolar disorder, mood stabilizer, switching, tolerance.

Introduction

Pharmacological strategies in bipolar disorder (BD) have widely broadened in the last few years due, to some extent, to the introduction of atypical antipsychotics in therapeutic options (Yatham et al., 2009; Liauw and McIntyre, 2010; Vieta et al., 2013). Currently, not only is there abundant evidence suggesting the efficacy of antipsychotics in acute mania, particularly for their fast onset effect (Nivoli et al., 2011b, 2013; Yildiz et al., 2011; Goikolea et al., 2013; Vieta and Valentí, 2013a), but antipsychotics are also a well-grounded treatment for acute depression and the prevention of relapses (Cruz et al., 2010; Frye et al., 2011; Nivoli et al., 2011a; Vieta et al., 2011; Grunze et al., 2013; Vieta and Valentí, 2013b).

Achieving an adequate pharmacological strategy in BD, as well as in other psychiatric disorders, occasionally implies changes among the different therapeutic alternatives (Fountoulakis et al., 2012; Grande et al., 2013). The reasons for switching may be diverse and involve: the particularities of individual patients with their own beliefs, expectations, adherence, brain biology and therapeutic alliance (Haro et al., 2011); the illness itself (Grande et al., 2012); the medication and its pharmacodynamics (Reinares et al., 2012); and, the environment (Buckley and Correll, 2008).

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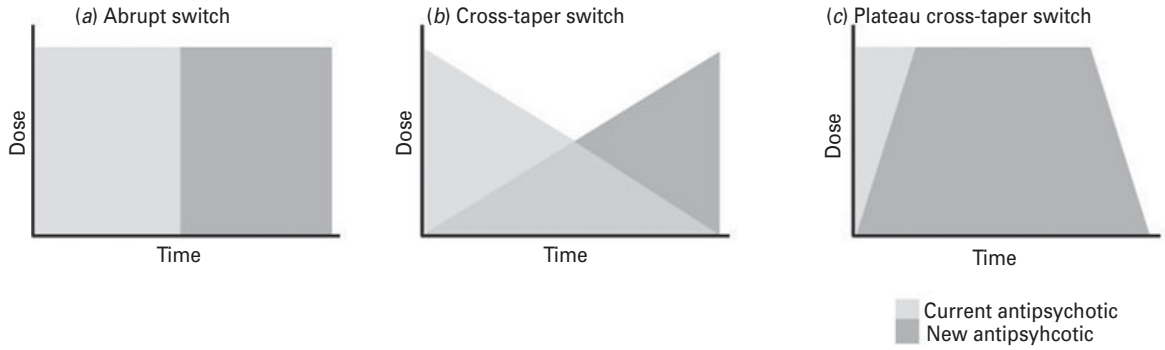

Fig. 1. Antipsychotic switching strategies (*a*) abrupt discontinuation of the current antipsychotic and immediate implementation of the new antipsychotic; (*b*) gradual cross-tapering of the current antipsychotic and the new antipsychotic; (*c*) continuation of the first antipsychotic at full dose while gradually tapering the new antipsychotic up to the optimal dose. When optimal dose is reached, proceed to the discontinuation of the first drug.

Knowledge about the strategies for dosing and switching of antipsychotics has been growing, based, in particular, on the literature on schizophrenia and schizoaffective disorder (Bernardo et al., 2011; Correll, 2011; Murru et al., 2011b; Stahl, 2013). In the field of BD, there is still a scarcity of evidence about this issue and, indeed, no specific clinical guidelines for the safe and effective interchange of these dissimilar drugs have been addressed. Only some indirect data and case reports have been published in this regard (Gardner et al., 1997; Rachid et al., 2004; Koener et al., 2007; Yang and Liang, 2011).

Careful antipsychotic dosing and judicious changes using appropriate switching strategies (Fig. 1) may help clinicians reduce discontinuation rates and unnecessary pharmacological modifications in BD (Buckley and Correll, 2008). This systematic review aims to provide a comprehensive update of the current literature in BD about the switching of antipsychotics, among them and between them and mood stabilizers, in acute and maintenance treatment. This information may be of special interest to clinicians, so as to determine adequate approaches for the optimal clinical management of patients with bipolar disorder.

Method

Data for this systematic review were collected with an advanced document protocol in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009; Urrútia and Bonfill, 2010). This proposal provides guidance for optimal reporting of systematic review protocols.

Data sources

A comprehensive, computerized literature search was conducted in the PubMed/Medline, PsycINFO, CINAHL database; the Cochrane Library and, the Clinicaltrials.gov web without language restrictions and up to January 9th, 2013. Our phrase and Boolean logic algorithms were [*'bipolar disorder'* AND (*switch* OR *switching* OR *change* OR *substitution* OR *shift*) AND (*antipsychotic* OR *antipsychotics* OR *aripiprazole* OR *asenapine* OR *chlorpromazine* OR *clozapine* OR *fluphenazine* OR *haloperidol* OR *olanzapine* OR *perphenazine* OR *quetiapine* OR *risperidone* OR *thioridazine* OR *ziprasidone*)] as well as [*'bipolar disorder'* AND (*switch* OR *switching* OR *change* OR *substitution* OR *shift*) AND (*antipsychotic* OR *antipsychotics* OR *aripiprazole* OR *asenapine* OR *chlorpromazine* OR *clozapine* OR *fluphenazine* OR *haloperidol* OR *olanzapine* OR *perphenazine* OR *quetiapine* OR *risperidone* OR *thioridazine* OR *ziprasidone*) AND (*lithium* OR *'valproic acid'* OR *carbamazepine* OR *oxcarbazepine*)]. Using the PRISMA statement, articles were selected based on title and abstract and, when necessary, on examination of the full text to assess relevance. Records retrieved through references of relevant articles, conference abstracts or registered clinical trials were screened for additional reports not previously identified. We also contacted authors to obtain information about studies. The first and last author of this study independently carried out the search. Any inconsistency was discussed and resolved. A search for published articles written by specific authors who had been working on clinical trials about atypical antipsychotics was also carried out.

Study selection

Records were reviewed using the following inclusion criteria: (1) original published longitudinal study reporting full results, (2) detailed description of the switching method and methodological background that evaluated BD using validated instruments or a semi-structured interview performed by a trained clinician based on DSM-IV-TR criteria, and (3) sample size >10 subjects diagnosed with BD. The following exclusion criteria were applied: (1) reports not published, (2) uncompleted studies, (3) case reports, (4) reviews, and (5) abstract with no results.

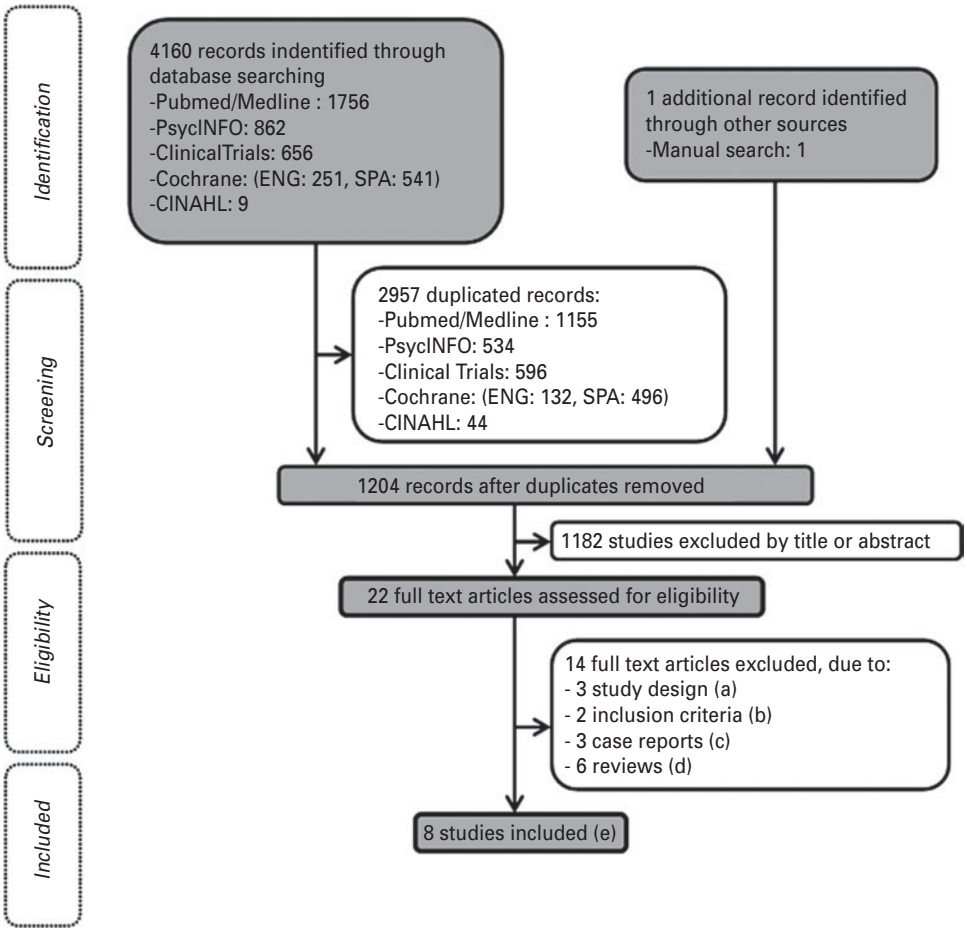

Fig. 2. PRISMA flow-chart of the studies considered and finally selected for review (Moher et al., 2009; Urrútia and Bonfill, 2010). (*a*) (Kluznik et al., 2001; Spurling et al., 2007; Wilting et al., 2008; Chandrasena et al., 2009; Di Sciascio et al., 2011). (*b*) (Bogan et al., 2000; Hilwerling et al., 2007). (*c*) (Rachid et al., 2004; Koener et al., 2007; Yang and Liang, 2011). (*d*) (Buckley, 2007; Buckley and Correll, 2008; Bobo et al., 2010; Liauw and McIntyre, 2010; Bernardo et al., 2011; Correll, 2011). (*e*) (Kluznik et al., 2001; Pae et al., 2004; Brown et al., 2005; Yatham et al., 2007; El-Mallakh et al., 2008; Weisler et al., 2011; Chen et al., 2012; Vieta et al., 2012).

Results

Using the aforementioned keywords, the search returned 4160 records whose title and abstracts were examined (Fig. 2). We excluded 4139 articles because they were duplicated records and did not meet *a priori* the selection criteria. One article was obtained by specific expert author search. We further identified 36 potentially relevant articles through cross-referenced bibliographies, which were thoroughly examined. Thirty-six did not fulfil inclusion criteria. We detected 8 out of 60 clinical trials apparently meeting the inclusion criteria. The NCT00246246 presented already published results, which were obtained by means of other databases (Yatham et al., 2007). In 4 completed clinical trials, the results were not available. Of the remaining 3 trials, 2 were ongoing and, in the other 1, the recruitment status was unknown. Twenty-five full text articles (Gardner et al., 1997; Bogan et al., 2000; Kluznik et al., 2001; Pae et al., 2004; Rachid et al., 2004; Brown et al., 2005; Savas et al., 2006; Buckley, 2007; Hilwerling et al., 2007; Koener et al., 2007; Spurling et al., 2007; Yatham et al., 2007; Buckley and Correll, 2008; El-Mallakh et al., 2008; Wilting et al., 2008; Chandrasena et al., 2009; Bobo et al., 2010; Liauw and McIntyre, 2010; Bernardo et al., 2011; Correll, 2011; Di Sciascio et al., 2011; Weisler et al., 2011; Yang and Liang, 2011; Chen et al., 2012; Vieta et al., 2012) were assessed for eligibility and in the end, 8 full text articles were included in the systematic review (Fig. 2) (Pae et al., 2004; Brown et al., 2005; Savas et al., 2006; Yatham et al., 2007; El-Mallakh et al., 2008; Weisler et al., 2011; Chen et al., 2012; Vieta et al., 2012). The characteristics of the articles selected are reported in Table 1.

Switching antipsychotics

Unlike other psychiatric disorders such as schizophrenia or schizoaffective disorder, scant literature is available in the field of BD concerning the switching of antipsychotics.

Table 1. Characteristics of the studies selected about switching antipsychotics and switching between mood stabilizers and antipsychotics

Study	Sample	Design	Duration (wk)	Outcome measures	Results summary	Comments
Switching antipsychotics						
Acute treatment						
(Pae et al., 2004)	18 manic BD-I inpatients intolerant to ris in combined treatment with mood stabilizer and ris	Open-label study with non-tapered switch from ris to quetiapine as add-on mood stabilizer treatment	3	*Efficacy*: CGI, YMRS *Safety*: BARS, SAS, DAI-10	Quetiapine was an effective and tolerated switching option for patients intolerant to ris with acute mania.	Prospective non-comparative study.
Maintenance treatment						
(Chen et al., 2012)	27 BD-I patients who evidenced adverse metabolic side effects (TG/HDL $\geqslant$ 3.5) (out of 52 patients)	Randomized, open-label study with cross-taper switch from A to aripiprazole (n=11) or ziprasidone (n=16)	52	*Effectiveness*: YMRS, HDRS, QLS, GAF *Safety*: weight, BMI, total cholesterol, HDL, LDL, TG, HbA1c, BARS, SAS, AIMS	Significant improvement in metabolic profile (ziprasidone: more favourable in total cholesterol and HDL values; aripiprazole: more favourable in TG/HDL ratio and HbA1c values)	Results were obtained in the whole sample of patients diagnosed with BD, SCH or SAD. No independent effect of diagnosis was found.
(Yatham et al., 2007)	49 BD I/II outpatients under combined treatment of mood stabilizer and OAA	Randomized, open-label trial with cross-switch from OAA (n=26) to LAI-ris (n=23) as an add-on mood stabilizer treatment	26	*Effectiveness*: number of interventions, CGI, YMRS, MADRS, HARS, EuroQol-5D, satisfaction VAS, time to intervention *Safety*: report of adverse events, laboratory test, vital signs, weight, BARS, SAS, AIMS	No significant differences in effectiveness, safety, tolerability or adverse events between groups LAI-ris showed significant reduction in means CGI and YMRS at follow-up, while OAA had significant reduction in HARS.	Not double-blind design. Small sample size.
(Savas et al., 2006)	12 noncompliant BD-I patients	Open-label study with cross-taper switch from OAA to first LAI (ris) as unique treatment or add-on mood stabilizer	26	*Efficacy*: BRMAS, HDRS, CGI	Significant improvement (achieving remission in all patients)	Only patients that showed full adherence to LAI-ris over 6 mth were included in the study.
(Vieta et al., 2012)	131 BD-I patients	Randomized, double-blind, placebo-controlled trial with cross switch arm from LAI-ris to olanzapine	78	*Efficacy*: Primary outcome: time to recurrence of any mood episode; Others: YMRS, MADRS, CGI *Safety*: weight gain, vital signs, ESRS	Time to recurrence of any mood episode was significantly longer with oral olanzapine compared to LAI-ris, especially for depressive mood episodes	Exploratory analyses Enriched study (LAI–ris responder-rich population)

(Brown et al., 2005)	19 BD-I/II patients on current substance abuse (out of 20)	Retrospective open-label study with cross-taper switch from A to aripiprazole	12	*Efficacy*: YMRS, HDRS, BPRS, substance craving VAS, dollars spent, substance use *Safety*: BARS, SAS, AIMS	Significant clinical improvement without changes in tolerability Alcohol dependence: reduction in money spent on alcohol and alcohol craving Cocaine: reduction in craving	1 of the 20 patients was diagnosed with SAD bipolar type. High attrition (13/20). Small sample.
Switching between mood stabilizers and antipsychotics						
Acute treatment						
(El-Mallakh et al., 2008)	38 BD-I patients non-responders to olanzapine in manic or mixed episode (out of 155)	Randomized, placebo-controlled trial with switch arm from olanzapine to carbamazepine extended-release capsules after washout of 2–5 days	3	*Efficacy*: Primary outcome: YMRS; Secondary outcome: HDRS, CGI	Clinical significance improvement almost achieved	Exploratory analyses. Underpowered analysis.
Maintenance treatment						
(Weisler et al., 2011)	176 quetiapine stabilized BD-I patients who had an affective event	Randomized, double-blind, placebo-controlled trial with switch arm from quetiapine to lithium	104	*Effectiveness*: Primary outcome: time to recurrence of any mood event; Secondary outcome: time to recurrence of a manic, depressive event, MADRS, YMRS, CGI, PANSS-P, SDS *Safety*: weight, BMI, SAS, BARS, AIMS, vital signs, physical, laboratory and ECG assessment	In patients stabilized during acute quetiapine treatment, continuation on this treatment significantly increased time to recurrence of any mood, especially depressive events compared to lithium. Overall rates of adverse events were generally similar between treatment groups	Enriched design resulting in a selection bias in favour of quetiapine

A: antipsychotics, AIMS: abnormal involuntary movements scale, BARS: Barnes akathisia rating scale, BD: bipolar disorder, BMI: body mass index, BPRS: brief psychiatric rating scale, BRMAS: Bech-Rafaelsen mania rating scale, CGI: clinical global impression-bipolar scale, DAI-10: drug attitude inventory shortened version-10, ECG: electrocardiography, ESRS: extrapyramidal symptoms rating scale, GAF: global assessment of functioning score, HARS: Hamilton anxiety rating scale, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein, HDRS: Hamilton depression rating scale, LAI: long acting injection, LAI-ris: risperidone long acting injection LDL: low-density lipoprotein, MADRS: Montgomery-Asberg depression rating scale, OAA: oral atypical antipsychotics, PANSS-P: positive and negative syndrome scale-positive symptom subscale, QLS: quality of life scale, ris: risperidone, SAD: schizoaffective disorder, SAS: Simpson-Angus scale, SCH: schizophrenia, SDS: Sheehan disability scale, TG: triglycerides, VAS: visual analog scale, YMRS: Young mania rating scale.

Not only have few articles on this topic been written but also the recruitment in most includes mixed samples of patients with BD, schizophrenia or other related psychotic disorders. The bibliography around this topic is principally focused on the comparison of the efficacy, effectiveness and safety among antipsychotics since they are the main reasons that lead to antipsychotic switching. These aspects have been assessed in acute and maintenance treatment, mainly considering the new atypical antipsychotics with oral and long-acting injectable (LAI) administration.

Acute treatment

Regarding treatment in acute mania, we found 1 article in which quetiapine was assessed as an add-on treatment in inpatients under mood stabilizer treatment and having displayed intolerance to risperidone (Pae et al., 2004). Intolerance was defined as the patients' subjective complaint and clinicians' observation of akathisia and dystonia assessed by the Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus Rating Scale (SARS). Eighteen patients completed this 3-wk trial. The Young Mania Rating Scale (YMRS) and Clinical Global Impression (CGI) scale scores significantly decreased from the time of admission to the end-point regardless of the mood stabilizer used. The SARS and BARS scores at baseline were significantly higher than at admission, showing an increase during the treatment with risperidone. The mean Drug Attitude Inventory short version-10 (DAI-10) score at baseline was significantly inferior compared with that upon admission. The SARS and BARS scores improved significantly at the end-point compared with baseline, with a mean change of 75% (1.8±0.9, $p<0.0001$) and 77.8% (1.4±0.8, $p<0.001$), respectively. The DAI-10 scores also changed to a positive response with statistical significance from baseline to the end-point (−1.7±0.7 *vs.* 0.8±0.9, $p<0.001$). On subgroup analyses according to the mood stabilizer, lithium and valproate did not show any significant differences in tolerability. Moreover, the use of benztropine, an anticholinergic drug for extrapyramidal side effects, significantly decreased from baseline to the end-point. While an improvement in extrapyramidal symptoms was depicted, other side effects such as sedation and gastrointestinal irritation were presented in more than half of the sample during the treatment with quetiapine. Moreover, one patient discontinued the trial due to excessive somnolence. The mean weight of the subjects increased significantly from baseline to the end-point (2.4±1.2 kg, $p<0.001$).

Maintenance treatment

Considering the side effects that may occur in long-term treatment, the metabolic and cardiovascular profiles of antipsychotics are of concern among patients and physicians, in particular, those drugs with a high histaminergic affinity such as clozapine and olanzapine (Buckley, 2007; De Hert et al., 2012). In fact, investigations on the metabolic profile of antipsychotics and treatment for the related side effects are currently ongoing. The risk of adverse metabolic effects varies considerably among antipsychotic drugs, aripiprazole and ziprasidone seeming to have a better metabolic profile (De Hert et al., 2012).

Chen et al. (2012) compared the metabolic profile and effectiveness of antipsychotic switching to aripiprazole or ziprasidone in a 52-wk follow-up. In this clinical trial, a mixed sample of patients diagnosed with BD, schizophrenia and schizoaffective disorder presenting adverse metabolic side effects were recruited. An adverse metabolic side effect was defined as a triglyceride/high-density lipoprotein (TG/HDL) ratio $\geqslant 3.5$. The most prevalent antipsychotic treatments were quetiapine, risperidone, and olanzapine. Patients were randomly assigned to treatment with aripiprazole or ziprasidone: 11 out of 24 patients with BD received aripiprazole at 5–30 mg/d and 16 out of 28 received ziprasidone at 40–160 mg/d. The new antipsychotic was titrated to reach target dose within 2 wk, according to the clinical effect (at the physicians' discretion) while the previous antipsychotic was progressively withdrawn. During the follow-up, significant improvements in body weight, body mass index, triglycerides (TG), high-density lipoprotein (HDL) levels and the TG/HDL ratio were registered. There were no differences between the 2 treatments during the monitoring except in body weight and glycated haemoglobin A1c (HbA1c), in which a greater reduction was detected in the ziprasidone and the aripiprazole groups, respectively. Following the switch to ziprasidone, an earlier reduction in body weight was observed compared to the aripiprazole group. The least square mean decrease in body weight at 52 wk was −13.97 (3.14) pounds for ziprasidone and −1.47 (3.57) pounds for aripiprazole ($p=0.004$). A sensitivity analysis, that excluded patients who received concomitant valproic acid and those who took therapy with antihyperlipidaemic and antidiabetic agents, supported the primary analysis for all lipid measures. Regarding HbA1c, it is of note that the effect on the glycaemic profile remained significant after excluding subjects who received concomitant valproic acid, but was no longer significant after excluding patients who initiated antidiabetic or antihyperlipidemic treatment. Although having recruited a mixed sample, no independent effect of the diagnostic group on anthropometric or metabolic measures over time was detected. Moreover, the change of antipsychotic did not interfere with the stability of the patients, showing no significant time or group per time interaction effects for most psychopathological measures except Global Assessment of Functioning scores that improved more in the aripiprazole group compared to the ziprasidone group.

Regarding the route of antipsychotic administration, studies on tolerability and effectiveness have also been carried out. Yatham et al. (2007) studied the oral and LAI administration of atypical antipsychotics (AA) as an

add-on maintenance mood stabilizer treatment over 6 mth. Patients were maintained on the previous mood stabilizer and were randomized to current AA or to LAI-risperidone (LAI-ris). Patients on LAI-ris treatment received a 25 mg injection every 2 wk for at least 6 wk with an initial 3 wk oral supplementation over their current oral AA. Of a sample of 49 subjects, 26 were randomized to oral AA, in particular quetiapine and olanzapine, and 23 to LAI-ris. No significant differences between treatment with LAI-ris or oral AA were found in either effectiveness or safety except that the LAI-ris group presented significant reductions in symptoms by means of the CGI and the YMRS scores while the oral AA group had significant reductions in the Hamilton Anxiety Rating Scale scores. Although 71% of the patients in the study reported at least 1 adverse event, only 3 subjects under LAI-ris and none under oral AA dropped out due to adverse events. A total of 5 patients in each group had an intervention for mood symptoms. In a retrospective study in non-compliant bipolar patients, Savas et al. (2006) also evaluated the efficacy of LAI-ris as the first LAI antipsychotic compared to other oral antipsychotic treatments. The previous oral antipsychotic was continued for 3 wk after the first injection of LAI-ris. Significant improvement was shown at the first month assessment and was maintained during the 6-mth follow-up. In fact, all the patients met criteria for remission. No patient had any manic or depressive relapse during the 6-mth treatment with LAI-ris compared with 1.42 mean episodes that occurred during the 6 mth prior to the antipsychotic switch.

Recently, Vieta et al. (2012) studied the efficacy and safety of LAI-ris for preventing recurrence of mood episodes in patients with BD-I in an international 18-mth randomized, double-blind trial. Patients who had not previously experienced recurrence during a 12-wk open-label trial with LAI-ris were included. Subjects were to discontinue treatment of all antipsychotics or mood stabilizers during this period. The patients were randomized to 3 treatment arms: (a) LAI-ris with variable doses from 25, 37.5 to 50 mg plus oral placebo (n=132); (b) oral and injectable placebo (n=135), and (c) injectable placebo with oral olanzapine (10 mg/d) (n=131) as a positive comparator. The primary efficacy end-point was time to recurrence of any mood episode for LAI-ris *vs*. placebo. This is the only controlled trial so far to show a significant advantage for a switching strategy over staying on the same drug after stabilization; hence, olanzapine was significantly more effective not only than placebo but also than long-acting injectable risperidone, despite the fact that all patients had been stabilized with risperidone. Importantly, the producer of risperidone, not olanzapine, sponsored the trial. The time to first recurrence of any mood episode, which was the primary outcome, did not show significant differences between LAI-ris and placebo, but there was a trend (p=0.056). Only time to an elevated mood episode was significantly longer in the LAI-ris arm compared with the placebo arm, with no significant differences in the depressive recurrences. The time to recurrence of any mood episode as well as an elevated mood episode or depressive episode was significantly longer with oral olanzapine than with placebo. An additional exploratory analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared to LAI-ris (p=0.001, stratified by region) and that the time to recurrence of an elevated mood episode (p=0.054, stratified by region) or depressive mood episode (p=0.004, stratified by region) was longer with oral olanzapine compared to LAI-ris, especially for depressive mood episodes. Focusing on tolerability, the most common adverse events occurring in patients receiving LAI-ris were weight increase, insomnia and amenorrhea, weight increase, somnolence and insomnia in the olanzapine arm. Due to adverse events, 5 patients in both the LAI-ris and olanzapine arms, discontinued the study while 2 patients abandoned the placebo group.

The practicability of an antipsychotic switch has also been evaluated in patients with BD and co morbid substance abuse disorders. Brown et al. (2005) studied the switch to aripiprazole from an atypical antipsychotic in 19 outpatients with BD and 1 with schizoaffective disorder, bipolar type. Most patients received quetiapine, olanzapine and risperidone. The change consisted in a progressive tapering of the previous antipsychotic treatment over a period of up to 6 wk, while aripiprazole was initiated at 15 mg/d and could be increased at any follow-up appointment up to 30 mg/d based on clinician judgment. This 12-wk follow-up pilot study suggested that patients with BD or schizoaffective disorders and co morbid substance abuse clinically benefited from the switch, showing a reduction in substance use and craving, without a modification in side effects. In 17 participants with current alcohol dependence, significant reductions in dollars spent on alcohol (p=0.042) and alcohol craving (p=0.003) were found. In 9 participants with cocaine-related disorders, significant reduction in cocaine craving (p=0.014) was shown.

Switching between mood stabilizers and antipsychotics

As the use of antipsychotics has become more widespread in BD, switching among these agents has become more common, in particular, since the introduction of the novel atypical antipsychotics with mood stabilizer properties. Due to this feature, studies have been designed to focus on the switch between mood stabilizers such as valproate, lithium or carbamazepine, to antipsychotics or vice versa in both acute and maintenance treatment.

Acute treatment

El-Mallakh et al. (2008) assessed the efficacy of extended-release carbamazepine as treatment for mania

or mixed episodes in patients with BD who had not previously responded to olanzapine (n=38), lithium or valproate by means of a *post-hoc* analysis of pooled data from 2, multi-centre, placebo-controlled 3-wk trials. Carbamazepine monotherapy was introduced after a washout period of 2–5 days. In subjects receiving extended-release carbamazepine the clinical scores significantly improved compared to subjects receiving placebo when they had previously taken lithium or valproate. Significance was not achieved if they were previously on olanzapine compared to the placebo group, but there was a trend (p=0.06).

Maintenance treatment

The effectiveness and safety of quetiapine monotherapy has been compared with switching to placebo or lithium (Weisler et al., 2011). In this 104-wk double-blind trial, patients who achieved stabilization for at least 4 wk of treatment with quetiapine were randomized to continue quetiapine or to switch to placebo or lithium, with lithemia ranging from 0.6 to 1.2 mEq/l. Time to recurrence of any mood event was significantly longer for the group treated with quetiapine *vs.* placebo and for the group treated with lithium compared to placebo. Compared to receiving lithium, the group of patients receiving quetiapine presented with significantly longer times to any mood or depressive event (HR=0.66, 95%CI: 0.49–0.88, p=0.005; HR=0.54, 95%CI: 0.35–0.84, p=0.006) suggesting that quetiapine is effective against both poles of the illness (Popovic et al., 2012). However, despite a significantly shorter time to recurrence when switched from quetiapine to lithium, patients receiving lithium ended up with similar recurrence rates to those staying on quetiapine, and lower recurrence rates than those switched to placebo, proving that the switch from quetiapine to lithium is feasible and effective.

Discussion

Despite the extensive work in the field of antipsychotics in BD and the expected prompt results of the ongoing clinical trials, a formally evaluated and clearly articulated approach of antipsychotic switching in BD is still lacking. Psychiatrists in BD currently rely on strategies recommended mainly for psychosis, since they are the most evidenced-based at present (Buckley and Correll, 2008). The current review covers the evidence available for switching among antipsychotics and between antipsychotics and mood stabilizers in BD.

Careful choice of the initial medication is advisable from the very beginning. For instance, an antipsychotic with adverse metabolic effects in a patient with a history of cardiovascular disease is not recommended, in spite of the efficacy of the treatment, since, in the long-term, the treatment may have a detrimental effect on the patient and treatment will have to be reassessed at some time. In line with this, the weight loss or the improvement in metabolic profile obtained by switching to aripiprazole or ziprasidone should be borne in mind (Goodwin et al., 2011; Kemp et al., 2012). In a retrospective chart review, Spurling et al. (2007) assessed the metabolic consequences of antipsychotics in a mixed sample, in which 5 out of 24 were patients diagnosed with BD. Metabolic modifications were immediately seen after the switch to aripiprazole from another second-generation antipsychotic: total cholesterol significantly decreased as did low-density lipoprotein and weight, regardless of whether patients were on antihyperlipidaemic treatment or not. In the study by Chen et al. (2012), this switch involved a weight loss of 6.4 (1.4) kg in the group of patients who switched to ziprasidone and 0.7 (1.6) kg in the group of patients who switched to aripiprazole. Although metformin, sibutramine, topiramate and reboxetine are recommended for routine use in clinical practice, they have demonstrated a modest, albeit statistically significant, mean short-term weight loss (Maayan et al., 2010). We not only have to take into consideration the metabolic effect itself of the antipsychotics but also the electrocardiologic consequences, such as sudden cardiac death (Grande et al., 2011). Di Sciascio et al. (2011) evaluated the differential effect on a potential marker of sudden cardiac death, such as QTc enlargement, between adding or switching antipsychotics. Despite the small sample size, the results indicated that an antipsychotic add-on significantly increased the QTc interval compared to an antipsychotic switch in patients diagnosed with BD and schizophrenia without medical co morbidities. Therefore, it is advisable to discern the optimal treatment and dose before considering a switch and to avoid the use of polypharmacy as far as possible.

When weighing up the advantages and disadvantages of antipsychotic switching, it becomes crucial to assess the efficacy profiles, receptor binding affinities, half-lives, tolerability and neurocognitive impact of the antipsychotics as well as the individual distinguishing features of each patient (Buckley, 2007; Popovic et al., 2011; Torrent et al., 2011). In the Pae et al., study (2004), the switch strategy might have been rather far from the ordinary clinical practice since the initial dose of quetiapine was 160.5±56.7 mg, a relatively high dose compared with conventional titration. Titration should be carried out until efficacy is achieved, until side effects appear or until the maximum recommended dose is reached (Murru et al., 2011a). In the randomized open-label clinical trial by Yatham et al. (2007), the pharmacodynamic profile of LAI-ris and the more stringent design of prescription in the LAI-ris group compared to the group treated with oral atypical antipsychotic may have biased the results in favour of the oral treatment. On the contrary, the i.m. administration route of an antipsychotic can improve the clinical outcome enhancing adherence, such as in the study carried out by Medori et al. (2005). Despite the presupposed bioequivalence of brand drugs and

generic drugs, studies about this topic have also been carried out. Kluznik et al. (2001) compared the efficacy of Clozaril® with the generic clozapine in a mixed sample in which patients diagnosed with BD were also recruited. In general, patients worsened on the switch from the brand name drug to generic clozapine, similar to what was described in a series of case reports in which the switch from clozapine to risperidone was assessed (Gardner et al., 1997).

The heterogeneity of the articles obtained in this systematic review from a methodological point of view should be taken into account (Colom and Vieta, 2011). The randomized controlled trials by Weisler et al. (2011) and Vieta et al. (2012) have an enriched design. In the Weisler study, a selection bias could have favoured the non-switching group (quetiapine-quetiapine), because all patients had previously responded to and tolerated quetiapine during the pre-randomization phase. In the Vieta trial, however, the outcome was better in the switching group (risperidone-olanzapine). Most of the advantage of olanzapine over risperidone was achieved in preventing depressive episodes, despite the fact that previous studies failed to show positive results in the prevention of depressive recurrences for olanzapine (Cipriani et al., 2010; De Fruyt et al., 2012). In another study cited, Savas et al. excluded patients that had not shown adherence to LAI-ris over 6 mth and had been diagnosed with substance abuse co morbidities (Savas et al., 2006) and, therefore selected the most adherent patients. In the Brown et al. study (2005), the attrition rate may have also contributed to the heartening results since only the data obtained from the 7 out of 20 participants that completed the 12-wk study were considered.

Antipsychotic switching is a current hot issue in the field of BD due to the established evidence of the effectiveness of antipsychotics in BD (Vieta et al., 2011; Yildiz et al., 2011). Controlled, randomized, double-blind, parallel-group trials are currently carried out to establish effectiveness of new psychopharmacological drugs for regulatory purposes (Vieta and Cruz, 2012). This systematic review identified very few studies that had the minimal quality to be considered informative, but the results indicate that switching from antipsychotics to mood stabilizers, and from antipsychotics to antipsychotics can be beneficial under certain circumstances. Specifically, quetiapine can be switched to lithium and long-acting injectable risperidone can be switched to oral olanzapine with little detriment, if any, of efficacy; moreover, metabolic safety and tolerability can be improved when switching from olanzapine, risperidone or quetiapine to aripiprazole or ziprasidone. As regards to the ideal strategy, abrupt switching is only justified in acutely ill patients or for emergency reasons. Plateau cross-taper is advised in patients who achieved remission but whom report tolerability issues related to the drug that helped to achieve remission. However, the evidence-base for these statements is rather weak. In the coming years, treatment switching needs to be more thoroughly addressed and investigated in studies properly designed to that effect in the field of bipolar disorder.

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M.B. has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of Adamed, Almirall, AMGEN, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Hersill, Janssen-Cilag, Lunbeck, Otsuka, Pfizer, Roche, Servier and has obtained research funding from: CIBERSAM, Generalitat de Catalunya, Ministerio de Ciencia e innovación, Ministerio de Educación (FIS, ISCIII), IDIBAPS, EUFP7.

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