Review

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Current Evidences on Psychopharmacology of Schizoaffective Disorder

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Schizoaffective disorder (SAD) is a psychotic disorder which has presented a certain nosological controversy. Apart from these difficulties, very few studies focused in SAD as a distinct condition from schizophrenia have been found. This lack of specifical studies on SAD results in a lack of specific evidence about treatment. Currently, its treatment is based mainly on the use of antipsychotics, although there are no specific treatment guidelines for SAD.

The objective of this review is to establish which are the most recommended treatments according to evidence available, considering clinical variables such as efficacy, safety, adherence, and tolerance as well as the role of these factors in different subtypes of SAD. This exhaustive review examines experimental and observational studies involving patients with a diagnosis of SAD.

It was concluded that more clinical trials performed exclusively on patients affected by SAD are needed. Paliperidone, the only drug with authorized use in SAD, is the one that has the highest quality of studies to support its use. Risperidone, olanzapine, aripiprazole and ziprasidone also have randomized clinical trials supporting their efficacy and safety. In treatment-refractory patients, there are observational studies indicating the usefulness of clozapine. Likewise, there is evidence from observational studies showing the usefulness of lithium and carbamazepine during the treatment maintenance phase. It is necessary to establish the role of combined treatment with mood stabilizers and/or antidepressants.

Keywords: Schizoaffective Disorder, Drug Therapy, Second Generation Antipsychotics, Paliperidone

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Evidencias actuales sobre el tratamiento psicofarmacológico del Trastorno Esquizoafectivo

El trastorno esquizoafectivo (TEA) es un trastorno psicótico que ha entrañado cierta controversia nosológica, junto a esta dificultad encontramos muy pocos estudios que aborden su tratamiento como una entidad diferente a la esquizofrenia. Estas dos dificultades dan como resultado la falta de evidencia específica sobre el tratamiento. Actualmente, el mismo, se basa principalmente en el empleo de antipsicóticos, aunque no existen guías específicas de manejo terapéutico.

Esta revisión tiene el objetivo de conocer cuáles son los fármacos que actualmente cuentan con estudios de mayor calidad científica que avalen su empleo según variables clínicas de efectividad, seguridad, adherencia y tolerancia, así como su papel en los diferentes subtipos de TEA y situaciones clínicas. Para ello, se realizó una revisión exhaustiva de estudios experimentales y observacionales que incluyeran pacientes con diagnóstico de TEA.

Se concluyó que son necesarios más ensayos clínicos realizados en pacientes con diagnóstico exclusivo de TEA. La paliperidona, el único fármaco con uso autorizado en el TEA es el fármaco que cuenta con mayor cantidad y calidad de estudios que avalen su uso. Risperidona, olanzapina, aripiprazol y ziprasidona también tienen ensayos clínicos aleatorizados que apoyan su eficacia y seguridad. En pacientes refractarios, hay estudios observacionales que señalan la utilidad de la clozapina. Así mismo, hay evidencia de estudios observacionales que señalan la utilidad de litio y carbamazepina durante la fase de mantenimiento. Es necesario establecer el papel del tratamiento combinado con reguladores del humor y/o antidepresivos.

Palabras clave: Trastorno Esquizoafectivo, Tratamiento Farmacológico, Antipsicóticos de Segunda Generación, Paliperidona

INTRODUCTION

Schizoaffective disorder (SAD) is a psychotic disorder in which criteria of moderate or severe intensity affective disorders coexist simultaneously with the nuclear symptoms of schizophrenia most of time and presenting psychotic symtomps a minimum of at least two weeks[1]. It is located in a continuum between both types of disorders or in a psychotic continuum[2,3]. Up to now, there has been some controversy about its nosological status, with low interobserver reliability (Cohen's kappa coefficient = 0.57)[4] which has led to both, diagnostic delay and lack of evidence on the specific treatment thereof. It is a relatively frequent disorder if we consider that it has an estimated prevalence of 0.32%, compared to 0.87% of schizophrenia[5].

The psychopharmacological treatment is a basic pillar of the global treatment of SAD and is based fundamentally, though not exclusively, on the use of antipsychotics, with mood regulators and antidepressants being used quite frequently.[6] Currently there are no specific clinical practice guidelines for the disorder and most of the information on its treatment is based on indirect evidence obtained mainly from studies of patients with schizophrenia and other psychotic disorders. As a consequence of this, there are no second generation antipsychotics with authorized indication except paliperidone[7]. Effective treatment is considered to be one that is capable of responding to acute symptoms and also serves as long-term maintenance therapy promoting recovery and functional capacity of the patient[8].

The objective of this bibliographical review is to know the best current evidence on the pharmacological treatment of SAD, trying to establish the profile of effectiveness, tolerance, safety and adherence of the different drugs and their role in the different SAD subtypes and the different clinical situations.

METHODOLOGY

Searching strategies

To carry out the review, the Web Of Science (WOS) search engine was used. A search of articles written in multiple languages was carried out using the following keywords: "schizoaffective disorder and drug therapy", "schizoaffective disorder and second generation antipsychotics", "schizoaffective disorder and paliperidone". The search reached up to the articles included until November 2018. A manual search was also carried out from lists of bibliographic references of texts. After obtaining the results of the initial search, duplicate citations were eliminated and after the analysis of the title and summary, the following inclusion and exclusion criteria were applied:

Inclusion Criteria

We included clinical trials and descriptive observational studies that measured effectiveness, tolerability, safety and adherence using validated scales, performed in populations that included patients with SAD and meeting the following requirements: 1. Diagnostic criteria for SAD according to the DSM-III-R, DSM-IV, DSM-V or the International Classification Diseases, ninth edition (ICD-9) and tenth edition (ICD-10). 2. A minimum study duration of 4 weeks.

Exclusion Criteria

1. Single cases for presenting a high risk of publication bias. 2. Studies that only present indirect evidence.

Subsequently, a complete reading of the selected articles was made and the aforementioned inclusion/exclusion criteria were applied again. Finally, with articles that met criteria, a critical narrative review was carried out incorporating the most relevant aspects (Figure 1).

RESULTS

A total of 1324 studies were identified, then 175 duplicate studies were eliminated, remaining 1149. After applying the inclusion/exclusion criteria in the title and the abstract, 1084 were eliminated, 65 articles were submitted to a full text reading. Finally, after checking again the inclusion/exclusion criteria, 30 studies were included. Table 1 summarizes the most important ones. 14 articles included data pertaining to double-blind randomized clinical trials (RCTs)[9-22], three of them were open clinical trials[23-25], In addition, 13 observational studies were found[26-38]. Tables 2, 3 and 4 summarize the main studies included according to the type of study and the time of follow-up.

Quality evidence (ECAs) was found on the following drugs: oral paliperidone and monthly injectable formulation, risperidone, olanzapine, aripiprazole and ziprasidone. We also found lower quality studies about clozapine, lithium carbonate, Valproic acid and other mood regulators.

Antipsychotics

Extended-release oral paliperidone

It was shown to reduce psychotic, affective symptoms and improve functionality in a double-blind, placebo-controlled RCT (n=311) with follow-up at 6 weeks. The efficacy and tolerability of extended-release oral paliperidone (PLP), both, monotherapy and in combination with mood stabiliz-

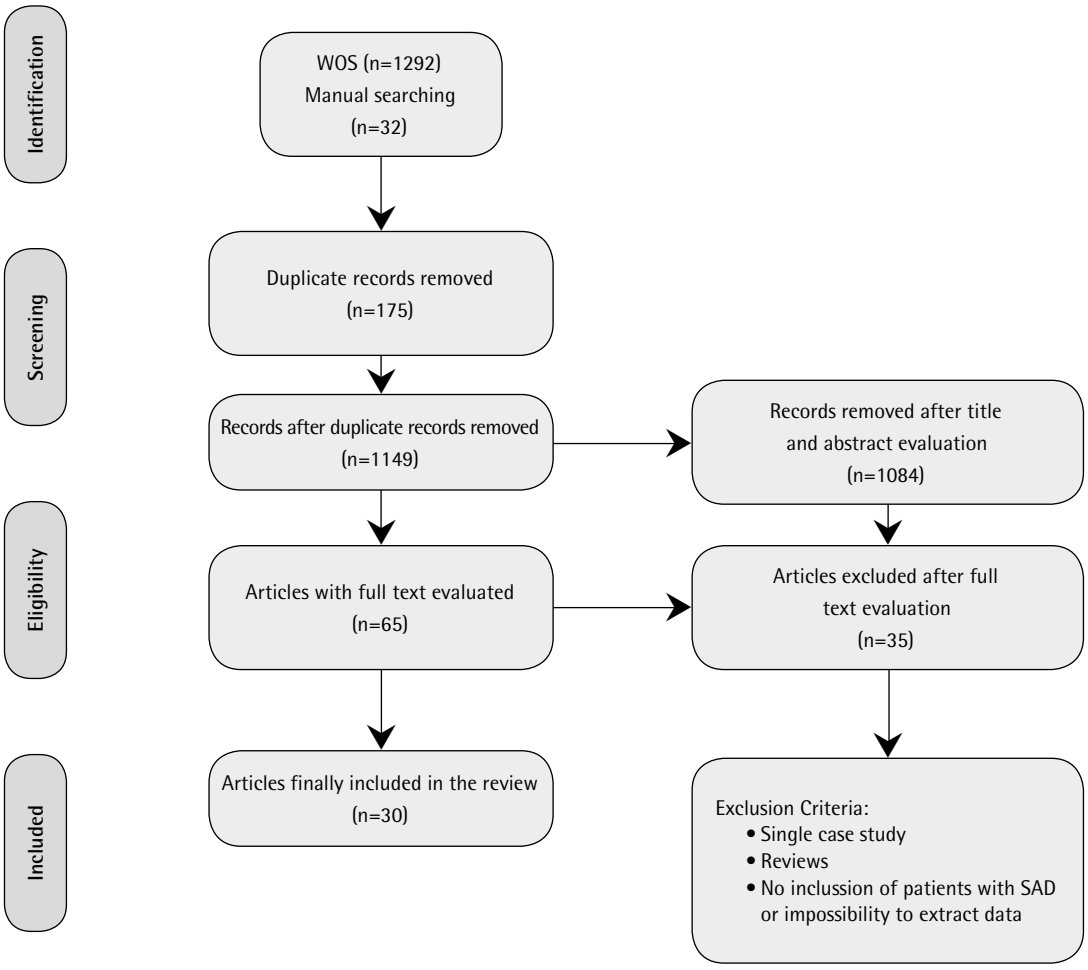

Figure 1 | *Flow diagram of the process of studies selection*

ers (MS) and/or antidepressants (ATD) versus placebo were evaluated[11]. The dose of PLP was 8.6(2.5) mg/day with a dose range between 3-12 mg/day. At the end of the study, there was a reduction in the mean score of -20(SD=1.3) and -10.8(SD=1.9) for PLP and placebo respectively, in the Positive and Negative Syndrome Scale (PANSS) in its five dimensions (positive, negative, anxiety/depression, disorganized thinking, hostility/excitement). There was also improvement in the domains of positive, negative and depressive symptoms of the severity scale of the GCI. In addition, those patients with predominantly manic or depressive symptomatology also showed improvement over placebo in both, the YMRS, -10.6(0.9) points with PLP and 5.7(1.2) points with placebo, as in the HAM-D, -10.2(0.7) points with PLP and -6.2(1.1) points with placebo. Regarding adverse effects, 65.4% of patients treated with PLP experienced adverse effects compared to 60% of the group treated with placebo. The only adverse effects that showed statistically significant differences against PLP were weight gain (7.5 PLP vs. 3.8% placebo), and hyperprolactinemia (2.8% patients with PLP)[11].

However, another 6-week double-blind RCT failed to demonstrate the superiority of 6 mg/day of extended-release oral paliperidone versus placebo, although it achieved this for doses of 12 mg/day[10]. When both studies were analyzed together[15], an improvement in psychotic, manic and depressive symptoms was found a week after starting treatment.

Paliperidone palmitate

The monthly formulation of paliperidone palmitate (PP), demonstrated in a double-blind RCT (n=334) of 15 months

Table 1 Duration and clinical variables of the main experimental and observational studies

ESTUDIO	EFFICACY/ EFFECTIVENESS	SAFETY	ADHERENCE	TOLERANCE	SHORT-TIME	LONG-TIME
1) CLINICAL TRIALS						
Fu et al, 2015[17]	X	X				X
Tohen et al, 2001[9]	X	X		X	X	
Canuso et al, 2010[11]	X	X			X	
Glick et al, 2009[12]	X	X		X	X	
Tran et al, 1999[20]	X	X		X	X	X
Keck et al, 2001[21]	X	X		X	X	
Janicak et al, 2001[19]	X	X		X	X	
Izaková et al, 2009[24]	X	X		X		X
Greil et al,1997[23]	X	X		X		X
2) OBSERVATIONAL STUDIES						
Joshi et al, 2016[33]	X		X			X
Baethge et al, 2004[36]	X					X
Ciaparelli et al, 2003[26]	X	X		X		X
Vieta et al, 2001[25]	X	X		X	X	
Lasser et al, 2004[31]	X	X		X		X
Maj 1987[30]	X					X

duration[17] be able to reduce relapse against placebo in both, monotherapy and adjuvant treatment. Compared with placebo, it significantly reduced the relapse time for psychotic, manic and depressive symptoms (p<0.001). Being the relapse rate 33.5% for placebo and 15.2% for monthly paliperidone. The risk of relapse was 2.49 times higher for the placebo than for the monthly paliperidone [HR=2.49; 95% CI (1.55-3.99); p<0.001]. For monotherapy, the risk of relapse was 3.38 times higher for placebo (p=0.002) and as an adjuvant treatment, 2.03 times higher for placebo (p=0.021). From the first week, there was an increase in the proportion of patients showing clinically significant improvements in psychotic, manic and depressive symptoms measured according a reduction of ≥10 points of the PANSS, ≥4 points on the HAM-D-21 scale and ≥6 points on the YMRS[14].

PP was also superior versus placebo improving functionality[17,18]. The most frequent adverse effects were weight gain (≥7%), 13% with paliperidone monthly compared to 6% with placebo, and hyperprolactinemia both in women (13.9% with paliperidone vs 5.8% with placebo) and in men (1.2% with placebo and 7.1% with paliperidone monthly)[17].

Oral Olanzapine

We found two cohorts of patients with SAD belonging to a double-blind RCTs where olanzapine was compared with haloperidol [9,20]. In the first of them[20], patients (n=300) were randomized to two groups: olanzapine (5-20mg/day) and haloperidol (5-20mg/day) and subsequently, those with good response at 6 weeks were followed for 1 year. Olanzapine had greater clinical efficacy, fewer side effects and fewer dropouts during the 6-week phase. In the annual follow-up period, patients with olanzapine continued to improve and experienced greater weight gain but less extrapyramidal effects than patients with haloperidol. In the second of the studies[9], a 6-week double-blind RCT including all SAD subtypes (n=77), olanzapine proved to be superior in the treatment of depressive symptoms measured using the Montgomery-Asberg depression evaluation scale, (MADRS) and cognitive symptoms (cognitive factor of the PANSS) of SAD compared to haloperidol. Although it was not possible to demonstrate superiority in manic symptoms, when it was measured with the score of manic symptoms of the Brief

Table 2 Short-term experimental studies on the pharmacological treatment of SAD

Study	Sample [diagnostic criteria]	Study Period	Type of Study	Groups of study	Measures	Results
Canuso et al, 2010[11]	Only SAD=311; [DSM-IV]	6 weeks	Double-blind, placebo-controlled RCT	PLP (3-12 mg/day) n=216 vs. Placebo n=95; 52% on treatment with ADT/MS	PANSS, CGI-S-SAD, YMRS, HAM-D-21	Improvement with PLP±ATD/MS compared to placebo. PANSS means for PLP and placebo: -20 (1.3) and -10.8 (1.9) respectively)
Tohen et al, 2001[9]	All types of SAD Subsample (n=177)	6 weeks	Double-blind RCT	OLP(n=120) vs HAL (n=57)	BPRS, PANSS and MADRS	OLP more effective on depressive and negative symptoms. Means difference for depressive symptoms OLP-HAL: -2.40(0.76); p=0.002
Janicak et al, 2001[19]	n=62 SAD patients. 29 depressive type and 33 mixed type.	6 weeks	Double-blind randomized	RIS n=30; mean dose 5.5(1.8) mg/day HAL n=32; mean dose 10.8(4.1) mg/day	PANSS, HAM-D-24, CARS-M	RIS and HAL effective on psychotic and manic symptoms. RIS superior on depressive symptoms. Reduction of 18(13) points versus 8 (11) points with HAL in HAM-D (t=2.5; p=0.02)
Keck et al, 2001[21]	Data analysis of two studies (n=115)	4-6 weeks	Double-blind, placebo-controlled RCT	ZIP (40-160 mg/day)	BPRS, CGI-S, MADRS, AIMS	ZIP 160 mg/day showed superiority versus placebo (p<0.01) in BPRS -16.3 (2.7); CGI-S -1.4(0.2) and BPRS mania -6.2(1). Adverse effects similar to placebo
Glick et al, 2009[12]	Data analysis of two studies (n=123)	4 weeks	Double-blind, placebo-controlled RCT	ARI 15-30 mg/day (n=123) and placebo (n=56)	PANSS, SAS, BARS, AIMS	ARI was superior to placebo in total PANSS score (-15.9 vs -3.4, p = 0.038) and positive subscale (-4.6 vs 1.0, p = 0.038). There were no statistically significant differences with placebo in relation to adverse effects

ATD Antidepressants; AIMS Abnormal Involuntary Movements Scale; ARI Aripiprazole; BARS Barnes Akathisia Rating Scale; BPRS Brief Psychiatric Rating Scale; CGI-S Clinical Global Impression-Severity Scale; CGI-SAD Clinical Global Impressions of Severity for Schizoaffective Disorder Scale; CARS-M Clinician-Administer Rating Scale for Mania; HAL Haloperidol; HAM-D-21Hamilton Rating Scale for Depression (21 items); MADRS Montgomery-Asberg Depression Rating Scale; MS Stabilizers; OLA Olanzapina; PANSS Possitive and Negative Syndrome Scale; PLP Extended-release paliperidone; RIS Risperidone; SAS Simpson-Angus Rating Scale; YMRS Young Mania Rating Scale; ZIP Ziprasidone.

Psychiatric Rating Scale (BPRS). Patients with olanzapine showed significantly fewer extrapyramidal symptoms[9].

Oral Risperidone

Risperidone was effective on psychotic and affective symptoms and was superior to haloperidol for depressive symptoms, being well tolerated. Thus, a 6-week double-blind RCT[19] comparing haloperidol (up to 20 mg/day) with risperidone (up to 12 mg/day) in 62 patients with SAD (29 depressive subtype and 33 mixed subtype) was found. There were no differences between both drugs in the reduction of psychotic and manic symptoms. In those patients with greater depressive symptomatology (HAM-D> 20), risperidone produced greater improvement than haloperidol. Specifically, 75% of patients with risperidone compared to 38% of patients with haloperidol reduced depressive symptoms by at least 50%. Risperidone was better tolerated than haloperidol. It also demonstrated its efficacy in psychotic and affective symptoms in an open study at 6 weeks[25] (n=112) in patients with bipolar or mixed type of SAD. In these patients, oral risperidone at an average dose of 4.7(2.5) mg/day produced an improvement of 18 points in the YMRS (p<0.0001), 19.9 points in the PANSS (p<0.0001), 6.6 points in the HAM-D (p<0.0001) and 0.9 points in the GCI scale (p<0.0001). The drug was well tolerated and adverse effects were mild.

Long-acting risperidone injection

In its long-acting formulation every 14 days, risperidone proved effective in the improvement of positive and negative symptoms, disorganized thoughts, anxiety/ depression and hostility/excitation measured with the PANSS in a stable

Table 3 Long-term experimental studies on the pharmacological treatment of SAD

Study	Sample [diagnostic criteria]	Study Period	Type of Study	Groups of study	Measures	Results
Fu et al, 2015[17]	SAD=334;[SCID DSM-IV]	25 weeks of open-label phase and 15-month relapse study	Double-blind, placebo-controlled RCT	Monthly PP (n=164; 78-234 mg/30 days); Placebo (n=170)	PANSS, YMRS, PSP, CGI-S-SCA, HAM-D-21	Significant reduction in the risk of relapse (33.5% vs 15.2%, p <0.001). Relapse risk for placebo [HR = 2.49; 95% CI (1.55-3.99); p <0.001]. The most important adverse effects were weight gain (≥7%), 13% with monthly paliperidone versus 6% with placebo and hyperprolactinemia
Tran et al, 1999[20]	SAD=300; [DSM-III-R]	6 weeks and then the responders were followed for 1 year	Double-blind RCT	Olanzapine (n=196;5-20 mg/day) and haloperidol (n=104; 5-20mg/day)	PANSS, BPRS, MADRS	At 6 weeks olanzapine was superior in reducing psychotic and depressive symptoms. After a year only in reduction of depressive symptoms
Greil et al, 1997[23]	SAD=90 (53% schizomanic subtype, 38% schizodepressive subtype, 9% unspecified); [DSM-III-R]	2.5 years	Open RCT	Li (N=43; 28±8 mmol/day) vs. CBZ (N=47; 643±179 mg/day)	GAS, Survival Analysis	Both were effective as maintenance therapy. CBZ was more effective in the depressive and unspecified type. CBZ obtained a lower rate of adverse effects (p<0.03) and greater tolerance (p<0.02)
Izáková et al, 2009[24]	Depressive subtype SAD= 52; [DSM-IV, CIE-10]	12 weeks	Open RCT	RIS (3.75-3.29 mg/day) vs. HAL (5.34-4.5 mg/day) combined with SERT (65.39-133.82 mg/day)	PANSS, GAF, HQLS, CDSS, CGI-I, DAI, PPS	Clinical improvement of psychotic symptoms with RIS against HAL+SERT according to PANSS score (Rm=0.47). In addition RIS lower rate of adverse effects and lower need for concomitant medication. Both treatments are comparable in the improvement of depressive symptomatology

ATD Antidepressants; BPRS Brief Psychiatric Rating Scale; Rm correlation coefficient of effect size of difference between grouped medians; CGI-I Clinical Global Impression-Improvement Scale; CGI-S Clinical Global Impressions of Severity Scale; CBZ carbamazepine; DAI Drug Attitude Inventory; GAS Global Assessment Scale; GAF Global Assessment of Functioning; HQLS Heinrich's Quality of Life Scale; HAL Haloperidol; HAM-D-21 Hamilton Rating Scale for Depression; OLA Olanzapine; Li Lithium; MS Mood Stabilizers; PANSS Possitive and Negative Syndrome Scale; ER-PLP Extended-release Paliperidone. Personal and Social Performance Scale; PP1M Monthly Palmitate of Paliperidone; RIS Risperidone; SADS-C Schedule for Affective Disorders and Schizophrenia-Change Version; YMRS Young Mania Rating Scale.

patients cohort (n=110) belonging to a study open with follow-up for 50 weeks. The mean score of the PANSS was reduced by an average of 9 ± 1.6 points at the endpoint of the study (p<0.001)[31].

Ziprasidone

When analyzing data from two double-blind RCTs, patients with SAD (n=115) treated with ziprasidone presented a dose-dependent clinical improvement[21]. The dose ranged between 40 and 160 mg/day. At a dose of 120 mg/day patients presented a greater clinical improvement than with placebo (p<0.05) when it was measured with ICG. In addition, 160 mg/day was better than placebo (p<0.05) when comparing the total scores of BPRS, manic subscale of BPRS and ICG. The patients suffered few side effects and were not related to the dose. There were no statistically significant differences in extrapyramidal side effects between ziprasidone and placebo.

Aripiprazole

In a combined analysis of two cohorts of patients with SAD (n=123) belonging to two double-blind RCTs of 4 weeks

Table 4 Observational studies on the pharmacological treatment of SAD

Study	Type of study	Sample description	Main results	Adverse Effects and adherence
Joshi, et al, 2016[33]	Descriptive observational	n=2713 (40.2 years; 52.7% women). n=1961 Incident SAD (72.3%) n=752 Prevalent SAD (27.7%)	The oral APS (especially RIS, QUET, ARI) were the most used (74.8%) even though their adherence rates are suboptimal (MPR, PDC). The rate of use of LAI is <2%. It is suggested that it could improve adherence and improve clinical results in SAD	Poor adherence (<50%) to common therapies in SAD (the most used: AP+AD/EA) measured according to MPR and PDC
Baethge et al, 2004[36]	Descriptive observational	n=49. 22 Depressive subtype Lithium n=41; Carbamazepine n=8 [DSM-IV/CIE-10]	Li and CBZ showed high effectiveness for the long-term prophylactic treatment in SAD at 6.8(6.1) years. The only variable related to the time of relapse was the onset age of SAD (HR:1.6; p<0.016). Great reduction of the hospitalization rate from 71 days to 11(p<0.001)	
Ciapparelli et al, 2003[26]	Descriptive observational	n=101. n=34 SCZ; n=30 bipolar subtype SAD; n=37 psychotic BD. [DSM-IV]	A high response rate to CLO (reduction of BPRS score>50%) is shown in subgroups of SAD and BD (90% and 83.8% respectively). GAF scale scores showed improvement in global functioning (p<0.01) in the 3 groups, being higher in the BD group	The SAD group showed the lowest discontinuation rates of CLO treatment
Vieta et al, 2001[25]	Observational	n=112; [DSM-IV/CIE-10] on treatment with RIS=4.7(2.5) mg/day and 6 weeks of follow-up.	At 6 weeks, reduction of the score with respect to the baseline in: PANSS 19.9 points (p<0.0001); 18 points in the YMRS (p<0.0001); 6.6 points in the HAM-D (p<0.0001) and 0.9 points in the CGI (p<0.0001)	Oral RIS was well tolerated with mild adverse effects
Lasser et al, 2004[31]	Observational	n=110 (DSM-IV). Stable patients were changed to LAI RIS /14 days during a 50 month follow-up	Improvement of the PANSS average score with respect to baseline -9(1.6); p<0.001 and in the dimensions of positive, negative symptoms, disorganized thoughts, anxiety/ depression and hostility/excitement	Significant decrease in extrapyramidal effects rates at 50 months compared to baseline
Maj, 1987[30]	Observational	n=54 (CIE-9) on treatment with Li during 2 years	Decrease in the number of relapses from 1.58 (0.64) to 0.99 (1.24) p<0.001	Not reported

ATD Antidepressants; APS Antipsychotics; ARI Aripiprazole; BD Bipolar Disorder; CBZ Carbamazepine; CLO Clozapine; GAF Global Assessment of Functioning; HAM-D Hamilton Rating Scale for Depression; HR Hazard Ratio; LAI Long Acting Injection; Li Lithium; MPR Medication Possession Ratio; MS Mood Stabilizers; PANSS Positive and Negative Syndrome Scale; PDC Proportion of Days Covered; QUET Quetiapine; RIS Risperidone; SCZ Schizophrenia; SAD Schizoaffective disorder; LAI RIS Long-acting injection risperidone; YMRS Young Mania Rating Scale.

duration, it showed to be effective, well tolerated and safe[12]. At 4 weeks of treatment, the improvement in the PANSS with respect to the placebo was -15.9 points versus -3.4 respectively (p=0.038), with the decrease in the positive subscale of the PANSS of -4.6 with aripiprazole versus -1 with placebo (p=0.027). There were no statistically significant differences with respect to placebo in metabolic variables, adverse effects and extrapyramidal symptoms. Prolactin decreased compared with placebo (-5.6 versus -1.3, p <0.001).

Clozapine

There is data from observational studies[26,27] and a RCT[13] (n=10) that show the usefulness of clozapine in patients

with refractory SAD. In a naturalistic study (n=30)[26] at 48 months of follow-up, 90% of patients with SAD responded to clozapine (p<0.01), experiencing a better clinical response and a lower discontinuation rate than those patients with schizophrenia. This better response from patients with SAD was also seen in a small RCT[13] (n=10) in which patients with SAD treated with clozapine and lithium improved the score in the GCI and the total score of the PANSS, including the cognitive dimensions and negative symptoms, without the patients with schizophrenia showed improvement.

Lithium, another mood stabilizers and antidepressants

Lithium and carbamazepine

Two studies[23,36] compared the usefulness of lithium and carbamazepine in the maintenance treatment of SAD. The most important of these was an open RCT[23] (n=90) in which the response of the different subtypes of the TEA to lithium and to carbamazepine was analyzed throughout a maintenance phase of 2.5 years. It concluded that both drugs were effective as maintenance therapy. With a higher dropout rate in the carbamazepine group (p<0.02), due to cutaneous reactions in the first months of treatment. In relation to the response of the different subtypes, the depressive and nonspecific showed a better response to carbamazepine in what refers to decrease hospitalizations (p=0.019) and recurrences (p=0.04). In relation to the adverse effects, a higher rate of mild-moderate type statistically significant was registered in the group treated with lithium (41.7% lithium versus 27.3% carbamazepine). Among those adverse effects most relevant, the majority of patients treated with lithium versus carbamazepine suffered tremor at some time (40 vs 5%, p <0.001), increased appetite (50 vs 21%, p=0.008), dry mouth (29 vs 8%, p=0.018), fatigue (55 vs 24%, p=0.005), polydipsia (55 vs 0%, p<0.0001), weight gain (61 vs 24%, p=0.001) and insomnia (55 vs 21%, p=0.002). Thus, long-term tolerance was shown to be higher in the carbamazepine group (p=0.02), which is reflected in the evaluation of patient satisfaction with treatment, where the scores were higher in the carbamazepine group (p=0.003). Therefore, both drugs are equally effective in long-term prophylactic treatment, except in the adverse effects rate, long-term tolerance and subjective satisfaction where carbamazepine seems to be superior to lithium. Furthermore, in the depressive and nonspecific subtype, carbamazepine was shown to be more effective, whereas in the manic subtype there were no differences between treatments.

An observational study[36] (n=49) also supported the effectiveness of lithium and carbamazepine in the maintenance treatment of SAD. A significant reduction in hospitalization rates was observed from 71 days to 11 days per year (p<0.001). The only predictive variable of the relapse time was the onset age of SAD (HR=1.6; p<0.016). Other naturalistic studies also supported its efficacy in reducing long-term relapses[30]. In conclusion, both lithium and carbamazepine were highly effective in the maintenance treatment of SAD.

Finally, it should be noted that some small studies reviewed the usefulness of the combination of lithium with clozapine in refractory patients[13] and its effectiveness in the mania of SAD[32].

Valproic Acid and another mood stabilizers

A naturalistic study[29] addressed the effectiveness of valproic acid in 20 patients with SAD, bipolar subtype, mean dose=1150(400) mg/day. There was improvement in the GCI scale in 75% of the patients (p=0.0001). None worsened or stopped treatment because of adverse effects.

A double-blind RCT[22] failed to demonstrate the efficacy of topiramate, mean dose=276(108) mg/day, range 100-400 mg/day, but significant weight loss at 8 weeks.

Finally, there were series of anecdotal cases that reported the possible effectiveness of lamotrigine in obsessive symptoms in SAD[34] and affective and paranoid symptoms[28].

Antidepressants

Regarding the group of antidepressants, an open RCT[39] (n=52), compared the effectiveness and safety of monotherapy with risperidone, mean dose=3.75-3.29 mg/day versus combined therapy with haloperidol, mean dose=5.34-4.5 mg/day plus sertraline, mean dose=65.39-133.82 mg/day, in women with SAD and depression. The efficacy, safety and tolerability of both treatments were evaluated. Both treatments were effective on depressive symptoms, neverthless risperidone was more effective on psychotic symptoms, improving the overall clinical impression, psychological, social and occupational functioning and the quality of life. Risperidone was also better tolerated overall although it experienced more early dropouts than the combination of haloperidol plus sertraline.

Adherence studies

An important observational study[33] evaluated the treatment patterns with antipsychotics used in the standard clinical practice of SAD in the United States. Adults diagnosed with SAD between 2009 and 2012 were included in the sample (n=2713) and were categorized into two cohorts: Incident SAD (patients without a diagnosis of SAD in the previous year)

n=1961 (72.3%) and SAD prevalent, n=752 (27.7%). Specifically, the adherence to the different antipsychotics was evaluated during a follow-up period of 12 months after diagnosis. 74.8% of the patients were on antipsychotic therapy, risperidone was the most commonly prescribed (23.9%), followed by quetiapine (21.4%) and aripiprazole (20.4%), all of them orally. The use of long-lasting injectable formulations (LAI) was less than 3%. A higher adherence rate was observed in patients with prevalent SAD compared to incident SAD. However, less than 50% of the patients showed adequate adherence to treatment with oral antipsychotics. This study concluded postulating the advisability of including LAI formulations in the usual treatment with antipsychotics in patients with SAD due to their potential higher adherence rate, which would improve the clinical results. Rates of poor adherence were also reported by other studies, specifically 72%[35] and 44%[38], being in both cases significantly worse than those of patients with bipolar disorder.

DISCUSSION

Currently, there is a scarce number of RCTs and observational studies on the treatment SAD, which makes it difficult to carry out clinical practice guidelines thereof. For this reason, the existing data and recommendations are very often based on indirect evidence and usually do not take into account the different subtypes of the disorder[40]. In addition, the scientific literature does not usually consider comorbidities such as autolytic ideas and substance abuse disorders that can significantly influence the results[41]. Nonetheless, some direct evidence on the treatment of SAD was gathered. Thus, paliperidone oral[11], PP monthly[17], ziprasidone[21] and aripiprazole[12] had double-blind RCTs with respect to placebo. Oral Risperidone[19] and olanzapine [9,20] also have double-blind RCTs with comparator haloperidol that support their use. Lithium and carbamazepine also showed their effectiveness in maintenance treatment[23]. There were few studies reporting data on adherence to treatment and the few who were found alerted of low adherence to treatment[33,35,38].

Antipsychotics

Oral paliperidone, the active metabolite of risperidone[42] and the only one with authorized indication for the treatment of SAD[7], demonstrated its efficacy in the treatment of psychotic and affective symptoms of SAD in the short time. As well in monotherapy as in combination treatment with antidepressants and mood regulators. Paliperidone palmitate monthly also proved to be effective in preventing relapse even beyond 12 months[17]. Paliperidone and PP also showed good tolerability[17,43]. Oral risperidone also showed to be a drug capable of controlling the psychotic and affective psychopathology of SAD, showing likewise a good tolerability[19,25]. A double-blind RCT at 8 weeks of follow-up (n=377) that included patients with both, schizophrenia and SAD[44] demonstrated the superiority of risperidone compared to olanzapine in controlling positive and anxious/depressive symptoms measured with the PANSS. Being olanzapine worse than risperidone in weight gain. In addition, LAI risperidone was also useful in maintenance therapy[31]. In a non-randomized clinical trial[45] at 6 months of follow-up that included patients with schizophrenia and other psychoses (n=1876), LAI risperidone at a dose of 25 mg/14 days showed to be able to decrease the PANSS score by 63.1±22. 8 points ($p<0.001$) in those patients in whom other antipsychotics had failed due to lack of efficacy or adherence. For all these reasons, paliperidone and risperidone could be used as monotherapy in acute phases. The existence of LAI formulations for both drugs makes them especially recommended in those patients with suboptimal results in which it is very likely that low adherence plays an important role. In this sense, some authors point out the importance of both, psychoeducation and the possible role of LAI formulations in improving the adherence of patients with SAD[46].

Other drugs with evidence to support its use in monotherapy given its overall efficacy and on the affective symptoms of SAD are olanzapine[9,20] and ziprasidone[21]. On one hand, a double-blind RCT[47] that compared olanzapine and risperidone in patients with schizophrenia and other psychotic disorders found significant differences in favor of olanzapine with a lower rate of extrapyramidalism, hyperprolactinemia, and sexual dysfunction. It could be a good option in the case of poor tolerance to paliperidone or risperidone due to extrapyramidal effects or hyperprolactinemia, provided that the weight gain is monitored. On the other hand, ziprasidone could also be a good option in case of suboptimal response or poor tolerance to olanzapine, risperidone or haloperidol[48], although its antidepressant effect is almost null[49]. It is a drug that should be taken into account in cases of cardiovascular risk, metabolic syndrome or hyperprolactinemia[50]. Aripiprazole is another candidate drug to be effective as monotherapy, having demonstrated its efficacy and safety[12], standing out for its excellent tolerability[52], with no influence on prolactin and very low impact on weight [53]. Indirect evidence from RCTs that included both patients with schizophrenia and SAD also supports their efficacy[54]. Furthermore, due to its antimanic[55] and antidepressant properties[49] demonstrated in bipolar disorder, it could be an effective drug for the affective symptoms of SAD, given that its metabolic effects are very scarce or null[51]. No quetiapine studies were performed exclusively in patients with SAD, but there is indirect evidence confirming their non-inferiority compared to risperidone on depressive symptoms of patients with schizophrenia and SAD, with a similar rate of adverse effects[56]. In addition, there is evidence of its antimanic[57] and antidepressant effect[49,58]. In cases of refractoriness, there is some evidence of the use of

clozapine, showing even better response than in patients with schizophrenia[13,26,27].

Mood stabilizers and antidepressants

In case of acute depressive symptomatology or affective symptoms, the use of mood regulators such as lithium and carbamazepine should also be considered, due to their efficacy and not inducing phase shifts, although their studies in patients with SAD are exclusively in the maintenance phase[23,26]. Finally, in relation to the use of antidepressants, it was not possible to demonstrate the superiority of the combination of antipsychotics and antidepressants versus antipsychotic treatment in monotherapy. Specifically, haloperidol plus sertraline did not prove to be more effective than risperidone in monotherapy on depressive symptoms, being risperidone better tolerated and with better overall results[24]. In another study, chlorpromazine was more effective than amitriptyline or the combination of both[32]. However, they can be useful in cases of poor response to antipsychotic treatment in monotherapy.

Treatment strategies

In relation to the treatment patterns, a multinational study[59] found that the most frequent was the use of an antipsychotic only (33.9%) followed by an antipsychotic plus a mood stabilizer (23.1%), an antipsychotic plus a antidepressant (27.7%) and in 7.7% of cases, an antipsychotic plus a mood regulator plus an antidepressant. Considering the available evidence, the most recommendable initial strategy would be the use of an antipsychotic with action on affective symptoms in monotherapy, preferably oral paliperidone or LAI, or other second generation antipsychotics such as risperidone, olanzapine, ziprasidone or aripiprazole, taking into account the existence of metabolic syndrome, possible adverse effects or other individual risk factors. In case of refractory affective symptomatology or poor control, combination therapy with mood regulators and/or antidepressants would be feasible since lithium and carbamazepine, in addition to regulating mood, are useful in the control of relapses. In case of resistance to antipsychotic treatment, clozapine should be considered. During the maintenance phase, PP monthly[17], LAI risperidone[31], olanzapine[20], clozapine[26], lithium and carbamazepine[23,30,36] showed to be effective in monotherapy. In relation to mood regulators, it is noteworthy that carbamazepine was more effective in the depressive subtype and was better tolerated than lithium[23]. A recent guide[41] advocates maintenance treatment with paliperidone oral and monthly PP given the low adherence of patients with SAD and maintains the absence of evidence about combined treatment with mood regulators and/or antidepressants.

LIMITATIONS

A standardized evaluation of the risk of biases of the included studies was not carried out and no recommendation grades were issued for the treatment, thus this review can not be considered a systematic review. However, it is a critical review that considers only direct evidence avoiding the confounding biases of all the studies that include both, patients with schizophrenia and patients with SAD.

CONCLUSIONS

RCTs are needed that address the treatment of SAD as a differentiated entity. Oral paliperidone and PP monthly, were the drugs with greater evidence in favor of its use. Oral and LAI risperidone, olanzapine, ziprasidone, aripiprazole and clozapine were treatments with some quality evidence endorsing their use. Lithium and carbamazepine demonstrated their usefulness in the prevention of relapses in the maintenance phase. First-line treatment is antipsychotic monotherapy. Studies are needed to establish the role of mood regulators and antidepressants as a combination therapy.

REFERENCES

1. OMS. CIE-10. Trastornos Mentales y del Comportamiento. Descripciones Clínicas y pautas para el diagnóstico. Madrid: Meditor; 1992.
2. Cheniaux E, Landeira-Femandez J, Telles LL, Lessa JLM, Dias A, Duncan T, et al. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. J Affect Disord. 2008;106(3):209-17.
3. Munoz-Negro JE, Ibanez-Casas I, de Portugal E, Ochoa S, Dolz M, Haro JM, et al. A dimensional comparison between delusional disorder, schizophrenia and schizoaffective disorder. Schizophr Res. 2015 Dec;169(1-3):248-54.
4. Santelmann H, Franklin J, Bußhoff J, Baethge C. Interrater reliability of schizoaffective disorder compared with schizophrenia, bipolar disorder, and unipolar depression – A systematic review and meta-analysis. Schizophrenia Research. 2016;176(2):357-63.
5. Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry. 2007 Jan;64(1):19-28.
6. Lindenmayer J, Kaur A. Antipsychotic Management of Schizoaffective Disorder: A Review. Drugs. 2016;76(5):589-604.
7. Gahr M, Koelle MA, Schoenfeldt-Lecuona C, Lepping P, Freudenmann RW. Paliperidone extended-release: does it have a place in antipsychotic therapy? Drug Design Development and Therapy. 2011;5:125-46.
8. Alphs L, Fu D, Turkoz I. Paliperidone for the treatment of schizoaffective disorder. Expert Opin Pharmacother. 2016; 17(6):871-83.
9. Tohen M, Zhang F, Keck PE, Feldman PD, Risser RC, Tran PV, et al. Olanzapine versus haloperidol in schizoaffective disorder,

bipolar type. J Affect Disord. 2001;67(1):133-40.
10. Canuso CM, Lindenmayer JP, Kosik-Gonzalez C, Turkoz I, Carothers J, Bossie CA, et al. A randomized, double-blind, placebo-controlled study of 2 dose ranges of paliperidone extended-release in the treatment of subjects with schizoaffective disorder. J Clin Psychiatry. 2010 May;71(5):587-98.
11. Canuso CM, Schooler N, Carothers J, Turkoz I, Kosik-Gonzalez C, Bossie CA, et al. Paliperidone extended-release in schizoaffective disorder: a randomized, controlled study comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. J Clin Psychopharmacol. 2010 Oct;30(5):487-95.
12. Glick ID, Mankoski R, Eudicone JM, Marcus RN, Tran Q, Assunção-Talbott S. The efficacy, safety, and tolerability of aripiprazole for the treatment of schizoaffective disorder: Results from a pooled analysis of a sub-population of subjects from two randomized, double-blind, placebo-controlled, pivotal trials. J Affect Disord. 2009;115(1):18-26.
13. Small JG, Klapper MH, Malloy FW, Steadman TM. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. J Clin Psychopharmacol. 2003; 23(3):223-8.
14. Fu DJ, Turkoz I, Simonson RB, Walling D, Schooler N, Lindenmayer JP, et al. Paliperidone Palmitate Once-Monthly Injectable Treatment for Acute Exacerbations of Schizoaffective Disorder. J Clin Psychopharmacol. 2016 Aug;36(4):372-6.
15. Fu D, Turkoz I, Bossie CA, Patel H, Alphs L. Rapid onset of treatment effects on psychosis, depression, and mania in patients with acute exacerbation of schizoaffective disorder following treatment with oral extended-release paliperidone. J Affect Disord. 2016;193:381-90.
16. Fu DJ, Turkoz I, Walling D, Lindenmayer JP, Schooler NR, Alphs L. Paliperidone palmitate once-monthly maintains improvement in functioning domains of the Personal and Social Performance scale compared with placebo in subjects with schizoaffective disorder. Schizophrenia Research. 2017;192:185-93.
17. Fu DJ, Turkoz I, Simonson RB, Walling DP, Schooler NR, Lindenmayer JP, et al. Paliperidone palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. J Clin Psychiatry. 2015 Mar;76(3):253-62.
18. Bossie CA, Turkoz I, Alphs L, Mahalchick L, Fu D. Paliperidone Palmitate Once-Monthly Treatment in Recent Onset and Chronic Illness Patients With Schizoaffective Disorder. J Nerv Ment Dis. 2017;205(4):324-8.
19. Janicak PG, Keck PE, Davis JM, Kasckow JW, Tugrul K, Dowd SM, et al. A double-blind, randomized, prospective evaluation of the efficacy and safety of risperidone versus haloperidol in the treatment of schizoaffective disorder. J Clin Psychopharmacol. 2001;21(4):360-8.
20. Tran PV, Tollefson GD, Sanger TM, Lu Y, Berg PH, Beasley CM. Olanzapine versus haloperidol in the treatment of schizoaffective disorder: Acute and long-term therapy. Br J Psychiatry. 1999;174(1):15-22.
21. Keck PE Jr, Reeves KR, Harrigan EP; Ziprasidone Study Group. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. J Clin Psychopharmacol. 2001 Feb;21(1):27-35.
22. Chengappa KNR, Kupfer DJ, Parepally H, John V, Basu R, Buttenfield J, et al. A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type. Bipolar Disord. 2007; 9(6):609-17.
23. Greil W, LudwigMayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, et al. Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: A randomised study. Eur Arch Psychiatry Clin Neurosci. 1997;247(1):42-50.
24. Izáková L, Andre I, Halaris A. Combination therapy or monotherapy for the depressed type of schizoaffective disorder. Neuropsychiatr Dis Treat. 2009;5:91-101.
25. Vieta E, Herraiz M, Fernandez A, Gasto C, Benabarre A, Colom F, et al. Efficacy and safety of risperidone in the treatment of schizoaffective disorder: Initial results from a large, multicenter surveillance study. J Clin Psychiatry. 2001;62(8):623-30.
26. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi M, et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic 48-month follow-up study. J Clin Psychiatry. 2003 Apr;64(4):451-8.
27. McElroy SL, Dessain EC, Pope HG, Cole JO, Keck PE, Frankenberg FR, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry. 1991 Oct;52(10):411-4.
28. Erfurth A, Walden J, Grunze H. Lamotrigine in the Treatment of Schizoaffective Disorder. NPS. 1998;38(3):204-5.
29. Bogan AM, Brown ES, Suppes T. Efficacy of Divalproex Therapy for Schizoaffective Disorder. J Clin Psychopharmacol. 2000 October;20(5):520.
30. Maj M. Lithium prophylaxis of schizoaffective disorders: a prospective study. J Affect Disord. 1988;14(2):129-35.
31. Lasser R, Bossie CA, Gharabawi G, Eerdekens M, Nasrallah HA. Efficacy and safety of long-acting risperidone in stable patients with schizoaffective disorder. J Affect Disord. 2004;83(2):263-75.
32. Brockington IF, Kendell RE, Kellett JM, Curry SH, Wainwright S. Trials of lithium, chlorpromazine and amitriptyline in schizoaffective patients. Br J Psychiatry. 1978 Aug;133:162-8.
33. Joshi K, Lin J, Lingohr-Smith M, Fu D, Muser E. Treatment Patterns and Antipsychotic Medication Adherence Among Commercially Insured Patients With Schizoaffective Disorder in the United States. J Clin Psychopharmacol. 2016;36(5):429-35.
34. Poyurovsky M, Glick I, Koran LM. Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. J Psychopharmacol. 2010 Jun;24(6):861-6.
35. Schoettle D, Schimmelmann BG, Conus P, Cotton SM, Michel C, McGorry PD, et al. Differentiating schizoaffective and bipolar I disorder in first-episode psychotic mania. Schizophr Res. 2012; 140(1-3):31-6.
36. Baethge C, Gruschka P, Berghofer A, Bauer M, Muller-Oerlinghausen B, Bschor T, et al. Prophylaxis of schizoaffective disorder with lithium or carbamazepine: outcome after long-term follow-up. J Affect Disord. 2004;79(1-3):43-50.
37. Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, et al. Clozapine for treatment-refractory mania. Am J Psychiatry. 1996 Jun;153(6):759-64.
38. Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F. Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. J Affect Disord 2013;151(3):1003-8.
39. Izakova L, Andre I, Halaris A. Combination therapy or monotherapy for the depressed type of schizoaffective disorder. Neuropsychiatr Dis Treat. 2009;5:91-101.
40. Baethge C. Long-term treatment of schizoaffective disorder: Review and recommendations. Pharmacopsychiatry 2003; 36(2):45-56.
41. Lindenmayer JP, Kaur A. Antipsychotic Management of Schizoaffective Disorder: A Review. Drugs- 2016 Apr;76(5):589-604.

42. Alphs L, Fu D, Turkoz I. Paliperidone for the treatment of schizoaffective disorder. Expert Opin Pharmacother. 2016; 17(6):871-83.
43. Canuso CM, Goldstein JM, Wojcik J, Dawson R, Brandman D, Klibanski A, et al. Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. Psychiatry Res. 2002;111(1):11-20.
44. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry. 2001 May;158(5):765-74.
45. Moller HJ, Llorca PM, Sacchetti E, Martin SD, Medori R, Parellada E, et al. Efficacy and safety of direct transition to risperidone long-acting injectable in patients treated with various antipsychotic therapies. Int Clin Psychopharmacol. 2005 May;20(3):121-30.
46. Vieta E. Developing an Individualized Treatment Plan for Patients With Schizoaffective Disorder: From Pharmacotherapy to Psychoeducation. J Clin Psychiatry. 2010;71:14-9.
47. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol. 1997 Oct; 17(5):407-18.
48. Alptekin K, Hafez J, Brook S, Akkaya C, Tzebelikos E, Ucok A, et al. Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study. Int Clin Psychopharmacol. 2009 Sep; 24(5):229-38.
49. Roberts RJ, Lohano KK, El-Mallakh RS. Antipsychotics as antidepressants. Asia Pac Psychiatry. 2016 Sep;8(3):179-88.
50. Stip E, Zhornitsky S, Moteshafi H, Létourneau G, Stikarovska I, Potvin S, et al. Ziprasidone for Psychotic Disorders: A Meta-Analysis and Systematic Review of the Relationship Between Pharmacokinetics, Pharmacodynamics, and Clinical Profile. Clinical Therapeutics. 2011;33(12):1853-67.
51. Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1. Schizophrenia Research. 2008; 101(1):273-86.
52. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.
53. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One. 2014 Apr 24;9(4):e94112.
54. Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry. 2003;60(7):681-90.
55. Muneer A. The Treatment of Adult Bipolar Disorder with Aripiprazole: A Systematic Review. Cureus. 2016 Apr 7;8(4):e562.
56. Di Fiorino M, Montagnani G, Trespi G, Kasper S. Extended-release quetiapine fumarate (quetiapine XR) versus risperidone in the treatment of depressive symptoms in patients with schizoaffective disorder or schizophrenia: a randomized, open-label, parallel-group, flexible-dose study. Int Clin Psychopharmacol. 2014 May;29(3):166-76.
57. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry. 2005 Jan;66(1):111-21.
58. Prieto E, Mico JA, Meana JJ, Majadas S. Neurobiological bases of quetiapine antidepresant effect in the bipolar disorder. Actas Esp Psiquiatr. 2010;38(1):22-32.
59. Canuso CM, Kosik-Gonzalez C, Sheehan J, Mao L, Kalali AH. Frequency of schizoaffective disorder in an International patient population with psychotic disorders using the Mini-International Neuropsychiatric Interview. Schizophrenia Research. 2010;118(1):305-6.