

Developing an Individualized Treatment Plan for Patients With Schizoaffective Disorder: From Pharmacotherapy to Psychoeducation

Eduard Vieta, MD, PhD

To develop an individualized treatment plan that addresses both psychotic and affective symptoms in patients with schizoaffective disorder, clinicians can take several steps. First, clinicians can confirm the diagnosis. In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* and in the *International Classification of Diseases, Tenth Revision (ICD-10)*, schizoaffective disorder is defined differently, but, diagnostically, the disorder falls on a spectrum between bipolar disorder and schizophrenia and can be divided into bipolar and depressive types. Next, clinicians can evaluate predictors of outcome. Outcomes can be predicted by previous functioning, number of previous episodes, persistence of psychotic symptoms, and level of cognitive impairment. Then, clinicians can use evidence from clinical trials to guide selection of acute and maintenance phase treatment. Although data are limited, direct and indirect evidence from clinical trials support pharmacologic and psychoeducational interventions. In bipolar type schizoaffective disorder, evidence supports the use of an atypical antipsychotic and a mood stabilizer or atypical antipsychotic monotherapy. In the depressive type of the disorder, the combination of an atypical antipsychotic and an antidepressant is probably the best choice, but an atypical antipsychotic and a mood stabilizer could also be used. In both types of the disorder, patient psychoeducation can be beneficial in the maintenance phase of treatment. Adherence to treatment is essential for optimal outcome, and, besides patient psychoeducation, long-acting injectable antipsychotics and psychoeducation for caregivers may also improve adherence. In refractory cases, electroconvulsive therapy is an option. (*J Clin Psychiatry* 2010;71[suppl 2]:14–19)

The diagnostic definitions for schizoaffective disorder vary, the treatment evidence is limited, and therapeutic guidelines are inconclusive. However, to formulate an individualized treatment plan, clinicians can confirm the diagnosis, evaluate predictors of outcome, and use evidence from clinical trials to select pharmacotherapy and psychoeducation for acute and maintenance phase treatment.

From the Bipolar Disorders Program and the Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain.

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Corresponding author: Eduard Vieta, MD, PhD, University of Barcelona, Director of the Bipolar Disorders Program, Clinical Institute of Neuroscience, Hospital Clinic, IDIBAPS, CIBERSAM, Villarroel 170, 08036 Barcelona, Catalonia, Spain (evieta@clinic.uib.es).

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CONFIRM THE DIAGNOSIS

Clinicians who suspect a diagnosis of schizoaffective disorder should confirm that patients do not fulfill criteria for either schizophrenia or bipolar disorder. The definitions for schizoaffective disorder differ in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*¹ and the *International Classification of Diseases, Tenth Revision (ICD-10)*,² but both show good long-term stability.^{3,4}

Schizoaffective disorder is divided into subtypes. In the *DSM-IV-TR*, patients who experience schizophrenic symptoms at the same time as manic episodes, mixed episodes, or major depressive episodes are said to have bipolar type schizoaffective disorder. If only depressive episodes occur with the schizophrenic symptoms, the patient is said to have depressive type schizoaffective disorder. The *ICD-10* identifies 3 types of schizoaffective disorder: manic, depressive, or mixed, according to the majority of mood episodes the person has. A not otherwise specified category is also available in the *ICD-10*. For more information on confirming the diagnosis, please see the article "Strategies for Making an Accurate Differential Diagnosis of Schizoaffective Disorder" by John M. Kane, MD, in this supplement.⁵

EVALUATE PREDICTORS OF OUTCOME

The next step is to evaluate clinical features of the patient's disorder that can predict outcome. Previous functioning,

FOR CLINICAL USE

- ◆ Confirm the diagnosis and type when developing an individual treatment plan for schizoaffective disorder.
- ◆ Evaluate predictors of outcome, and assess current and future barriers to adherence to treatment.
- ◆ Select treatments for the acute and maintenance phases of schizoaffective disorder based on the available evidence, and implement psychoeducation at the appropriate time.
- ◆ Use long-acting injectable antipsychotics or electroconvulsive therapy if appropriate.

number of episodes, nature of psychotic symptoms, and cognitive impairment can predict outcome. Assessing these features is critical in establishing a treatment plan, predicting how the illness may develop, and addressing near-future problems.

Previous Functioning

Patients with adequate functioning at baseline are more likely to have outcomes such as minimal psychiatric symptoms and little functional impairment than those patients with poor functioning at baseline.⁶ The functional levels of patients with schizoaffective disorder may be better than those with schizophrenia but worse than those with bipolar disorder. When personal autonomy and occupational adaptation were followed prospectively for 3 years in 138 outpatients with schizoaffective disorder, schizophrenia, and bipolar I disorder, all groups showed impairment.⁷ An intermediate number of participants with schizoaffective disorder had adequate outcomes relative to those with schizophrenia or bipolar disorder.

Number of Episodes

The more episodes of schizoaffective disorder that a patient has experienced, the more difficult achieving full recovery from the present episode is likely to be. Marneros and colleagues⁸ evaluated 101 patients who had had the disorder for a mean period of 25.5 years. Worse psychosocial deficits—including downward occupational mobility, premature retirement, impaired autonomy, and unattained social development—were associated with a higher number of episodes during the course of illness.

Nature of Psychotic Symptoms

The persistence and characteristics of psychotic features can predict outcome. Some patients with schizoaffective disorder have permanent prominent psychotic symptoms, and their disorder is closer to the syndrome of schizophrenia, although they have the mood swings that are a core feature of schizoaffective disorder. The *DSM-IV-TR* states that a period of schizoaffective illness (with active or residual psychotic symptoms) may last for years without a period of recovery.^{1(p319)} Other patients with schizoaffective disorder have prominent psychotic symptoms only during

mood episodes, and, between mood episodes, they have only low-level psychotic symptoms. Patients with less persistent psychotic symptoms have a better prognosis than patients with more persistent psychotic symptoms.⁸

The presence of psychotic features during the index episode of bipolar disorder has been found to increase the risk of relapse. Among 24 patients with bipolar disorder who had recovered from an index episode of mania and were followed for 4 years, 20% of those with psychotic features at baseline remained in remission, whereas 78% of patients without psychotic features at baseline remained well.⁹ Unlike in bipolar disorder, psychotic symptoms are part of the schizoaffective diagnosis, meaning that clinicians should be especially on guard for relapse in these patients.

Psychotic symptoms may be appropriate to the mood episode the patient is experiencing (ie, mood-congruent) or inappropriately matched to the mood (ie, mood-incongruent). Among 210 patients with schizoaffective disorder, schizophrenia, and affective disorders with psychosis who were followed for 10 years,¹⁰ participants who had mood-incongruent psychotic symptoms during the acute phase were more likely to have poor outcomes (eg, poor psychosocial functioning and the presence of major symptomatology) than those with mood-congruent psychotic symptoms.

Level of Cognitive Impairment

Cognitive impairment is a critical feature to evaluate because it is closely related to functioning. In patients with chronic schizophrenia or schizoaffective disorder, performance on a battery of neurocognitive tests (especially verbal working memory) better predicted employment status than did clinical symptoms.¹¹ In a population-based study,¹² results of premorbid intellectual, behavioral, and language functioning tests in adolescents who later developed schizoaffective disorder showed that their only significant impairments relative to matched controls ($P < .05$) were nonverbal abstract reasoning and visual-spatial problem-solving abilities. Cognitive impairment may be higher in schizoaffective bipolar patients than in nonpsychotic bipolar patients.¹³

USE EVIDENCE-BASED PHARMACOTHERAPY

The evidence base for the treatment of schizoaffective disorder with pharmacotherapy is limited, and most of the controlled data come from trials that included patients with schizoaffective disorder and those with schizophrenia. The studies described below are ranked by quality. Scant data are available for compounds not included here, such as conventional antipsychotics, lithium, and valproate. Indirect evidence of efficacy of antipsychotics for manic and depressive symptoms and of nonpharmacologic treatments is available from trials in patients with schizophrenia and bipolar disorder.

Specific Stand-Alone Placebo-Controlled Trial: Paliperidone

Only 1 placebo-controlled trial¹⁴ has addressed the efficacy and tolerability of a specific drug in patients with acute schizoaffective disorder. Lower and higher doses of

paliperidone extended-release were compared with placebo in 316 randomly assigned subjects with schizoaffective disorder over 6 weeks. As shown in Figure 1, mean Positive and Negative Syndrome Scale (PANSS) scores improved significantly with the higher dose versus placebo (-32.4 ± 2.1 vs -24.1 ± 2.1 , $P = .003$). Paliperidone was well tolerated; headache and tremor were the adverse effects that occurred in more than 10% of participants. Safety measures showed greater increases in body weight and prolactin levels from baseline to endpoint with the active drug than with placebo.

Pooled Analysis/Subanalysis: Ziprasidone and Aripiprazole

The second rank of evidence is efficacy studies of medications for schizophrenia in which patients with schizoaffective disorder were included and data were pooled or subanalyzed for the subsample with schizoaffective disorder.

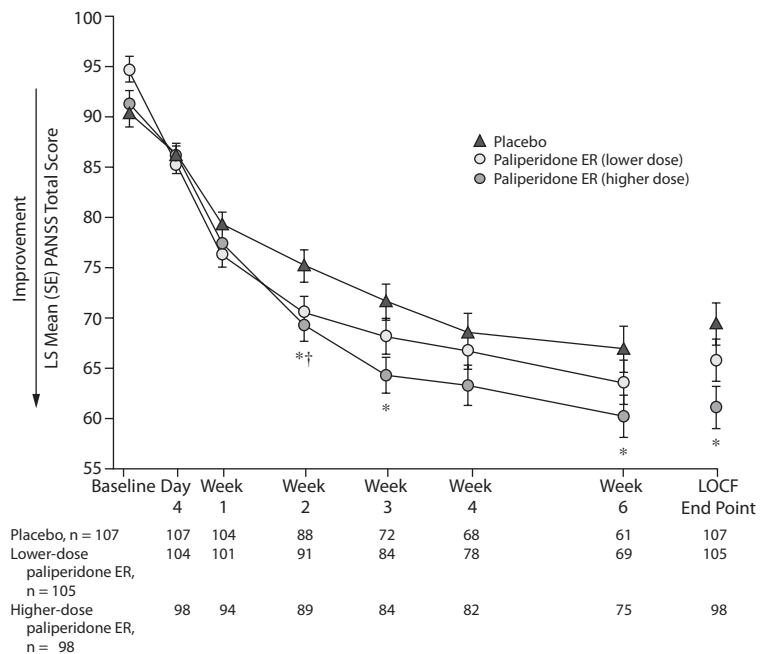
In one analysis,¹⁵ data were pooled from 2 double-blind, placebo-controlled, parallel-group, multicenter studies of 115 patients with an acute episode of schizoaffective disorder. The subjects were randomly assigned to treatment with 1 of 4 doses of ziprasidone or with placebo for 4 to 6 weeks. Results showed dose-related improvement from baseline to endpoint compared with placebo on several rating scales, including the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions-Severity scale ($P \leq .01$) (Figure 2). Psychotic and affective symptoms were reduced, but, at the doses studied, the effect appeared to be more robust for manic symptoms than depressive symptoms. The side effect burden was low; pain, headache, dyspepsia, and somnolence were most frequent.

Another pooled analysis¹⁶ examined 2 subsets of subjects with schizoaffective disorder (N = 179) who were treated for 4 weeks with aripiprazole or placebo. Improvement with aripiprazole was statistically significant versus placebo on PANSS total scores and the Positive subscale scores ($P < .05$), but improvement in the PANSS Negative subscale score did not reach statistical significance. The most common adverse effects in the aripiprazole group were headache, agitation, insomnia, and anxiety.

Adjunctive Placebo-Controlled Trial: Topiramate

One small placebo-controlled, double-blind pilot study¹⁷ examined, but did not support, clinical efficacy for adjunctive topiramate in 48 patients with a diagnosis of schizoaffective disorder, bipolar type. Topiramate was added to treatments that included mood stabilizers, such as lithium and/or valproate, and typical or atypical antipsychotics. By week 8 of treatment, adjunctive topiramate showed no increase in efficacy versus placebo as measured by PANSS total scores or secondary measures. No major safety or tolerability issues were found.

Figure 1. Mean PANSS Total Score Over Time (ITT analysis set) in Schizoaffective Disorder Patients Treated With Paliperidone Versus Placebo^{a,b}



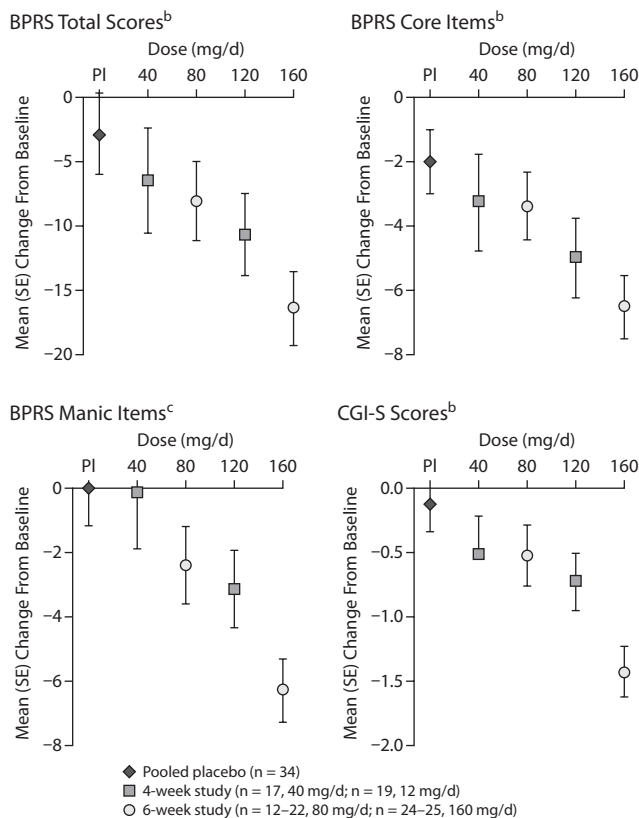
^aReprinted with permission from Canuso et al.¹⁴
^bDay 4 through week 6 based on observed scores using repeated-measures ANCOVA; LOCF end point comparison from an ANCOVA model.
 * $P < .05$, higher-dose paliperidone ER vs placebo.
 † $P < .05$, lower-dose paliperidone ER vs placebo.
 Abbreviations: ANCOVA = analysis of covariance, ER = extended-release, ITT = intent to treat, LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome Scale, SE = standard error.

Comparative Trials: Olanzapine or Risperidone Versus Haloperidol

Two trials compared the efficacy of an atypical antipsychotic versus the active control haloperidol in patients with schizoaffective disorder. No placebo arm was used.

Olanzapine was compared with haloperidol in a double-blind, prospective, 6-week study¹⁸ that examined 300 individuals with schizoaffective disorder (both bipolar type and depressive type). Up to 1 year of double-blind maintenance therapy was available to responders, and 110 patients entered this phase. As shown in Figure 3, in the acute phase of treatment, the bipolar type subgroup had statistically significantly greater mean changes from baseline ($P < .05$) with olanzapine versus haloperidol on several measures of efficacy; patients with the depressive type of illness did not show significantly different mean changes in efficacy scores between the 2 treatments. Irrespective of illness subtype, however, rates of response (ie, a $\geq 40\%$ reduction in BPRS total score from baseline) to olanzapine (51% for bipolar type and 49% for depressive type) were significantly greater than those to haloperidol (30% for bipolar type and 23% for depressive type; $P < .005$). Increased appetite was the only adverse event reported statistically significantly more often by those taking olanzapine than haloperidol. Subjects taking haloperidol reported akathisia, nervousness, tremor, vomiting, anorexia, dyskinesia, and increased salivation

Figure 2. Dose-Related Reduction in BPRS and CGI-S Scores in Patients With Schizoaffective Disorder Treated With Ziprasidone in 2 Placebo-Controlled Trials^a



^aReprinted with permission from Keck et al.¹⁵

^b $P = .01$, dose-response.

^c $P < .001$, dose-response.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity scale, PI = placebo, SE = standard error.

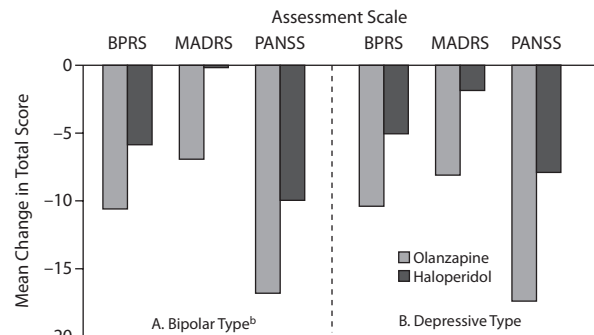
more often than those taking olanzapine. Improvement continued during the maintenance phase of treatment, including a significantly greater mean change ($P < .05$) with olanzapine versus haloperidol on the Montgomery-Åsberg Depression Rating Scale total score among patients with the depressive type of schizoaffective disorder.

A double-blind, randomized, prospective, 6-week study¹⁹ compared risperidone and haloperidol. The 2 agents were similarly effective in reducing psychotic and manic symptoms in 62 patients with schizoaffective disorder. In a subset of 37 subjects with more severe depression at baseline according to Hamilton Depression Rating Scale (HDRS) scores, risperidone produced at least a 50% mean improvement in 75% of patients taking it, while haloperidol produced similar results in 38% of subjects. Risperidone was better tolerated than haloperidol.

Observational Studies: Risperidone and Ziprasidone

In a 6-month open study²⁰ of patients with an acute episode of bipolar disorder or schizoaffective disorder, bipolar type, risperidone was used as monotherapy or as an adjunct to a continued mood stabilizer or antidepressant. In the 183 patients with schizoaffective disorder, significant improvement

Figure 3. Mean Change in Total BPRS, MADRS, and PANSS Scores in Patients With Schizoaffective Disorder Treated With Olanzapine or Haloperidol^a



^aData from Tran et al.¹⁸

^bAll comparisons were significant ($P < .05$).

Abbreviations: BPRS = Brief Psychiatric Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

in Young Mania Rating Scale and HDRS scores from baseline ($P < .0001$) occurred in those treated with risperidone. Improvement reached significance by day 7 and remained so at 6 months. Side effects were typically mild or moderate, and drowsiness and weight increase were most common.

In an open-label 12-week prospective study²¹ of 276 patients with schizophrenia or schizoaffective disorder who switched to ziprasidone from a first- or second-generation antipsychotic or combination of both, ziprasidone was associated with significant improvement in BPRS scores ($P < .001$). Serious adverse events occurred in 14% of patients. Psychotic symptoms were the most common adverse event and individual cases of other adverse events occurred.

Adherence to Treatment

Nonadherence to treatment contributes to reduced response rates and poor outcome.²² Clinicians should ensure that patients have no concerns or beliefs about the need for therapy or the efficacy of treatment that will prevent them from taking medication.²³ Individual treatment plans should address current and future barriers to adherence, eg, illness awareness and insight, tolerability of current treatment, and potential safety problems. Contributors to poor adherence, such as substance abuse and personality disorders,²⁴ should also be taken into account. In patients who are nonadherent or partly adherent to medication, long-acting injectable antipsychotics can be considered.²⁵ Psychoeducation, delivered when the patient is free from acute symptoms, may help with adherence. For more information about adherence, please see the article "Strategies for Improving Treatment Adherence in Schizoaffective Disorder" by Goff and colleagues in this supplement.²⁶

IMPLEMENT PSYCHOTHERAPY

A psychoeducational approach to psychotherapy for patients and caregivers may not only improve adherence and illness awareness but also increase detection of relapse signs

and thereby improve outcomes. No studies of psychoeducation are available specifically for schizoaffective disorder, but a 9-week psychoeducational program²⁷ in 103 outpatients with schizophrenia and schizoaffective disorder was found to improve patients' concept of and knowledge about their illness as well as their quality of life. These improvements were found to last 12 months whether or not a series of booster sessions was provided. Compared with treatment as usual, a 24-week psychoeducational intervention²⁸ that focused on illness management was found to improve knowledge of illness but not symptoms, adherence, or global functioning in 71 patients with schizophrenia and schizoaffective disorder. In a study²⁹ that provided 8 psychoeducation sessions over 4 to 5 months separately to both 236 inpatients (with schizophrenia and schizoaffective disorder) and their family members, rehospitalization rates after 12 and 24 months among those with 2 to 5 previous psychotic episodes were significantly lower ($P < .05$) with the intervention than with treatment as usual.

Studies of psychoeducation in bipolar disorder may apply to schizoaffective disorder patients. Group psychoeducation for patients with bipolar I and II disorder improved outcomes.³⁰ In 120 patients who were in remission, taking pharmacologic treatment, and receiving standard psychiatric care, those who received 21 sessions of group psychoeducation had significantly fewer recurrences of the disorder compared with participants who received 21 unstructured group meetings (67% vs 92%, $P < .001$) and a longer time to any recurrence. During the 2-year follow-up, the number and length of hospitalizations were significantly lower in the treatment group than in the control group ($P < .05$).

Group psychoeducation for caregivers of outpatients with bipolar disorder reduced the risk of recurrence of mania and may do so in schizoaffective disorder. In a study³¹ of 113 outpatients who lived with caregivers, received medication, and were euthymic, the caregivers either received 12 group psychoeducation sessions that concentrated on knowledge of the disorder and instruction in coping skills or did not receive the intervention. Over the intervention and 12-month follow-up periods, the percentage of patients with any mood recurrence was reduced ($\chi^2 = 6.53$, $P = .011$) and relapse-free intervals were lengthened (log rank $\chi^2 = 4.04$, $P = .044$) in those whose caregivers received psychoeducation compared with controls. The reductions were statistically significant in patients with hypomanic or manic recurrences ($\chi^2 = 5.65$, $P = .017$).

Compliance therapy was shown to be effective in patients with schizophrenia or depression²⁴ but not in patients with schizoaffective disorder.³² Forms of psychotherapy that seem to have efficacy in patients with schizoaffective disorder include cognitive-behavioral social skills training,³³ functional adaptation and skills training,³⁴ and vocation-enhanced cognitive-behavioral therapy.³⁵

INDIVIDUALIZE THE TREATMENT PLAN

Developing a personalized treatment plan requires merging the evidence for particular treatments with the

individual patient's symptoms and treatment issues. When data are limited, as they are for treatment for schizoaffective disorder, the treatment paradigm shifts from treating the syndrome to treating the psychotic, manic, and depressive symptoms using evidence from schizophrenia and bipolar disorder trials as well as schizoaffective disorder trials. Treatment plans need to be tailored to manage the bipolar type or depressive type of schizoaffective disorder in the acute and maintenance phases.

Schizoaffective Disorder, Bipolar Type

Antipsychotics should be given when psychosis and manic symptoms are prominent. Treatment is also required for depressive symptoms, and data from bipolar disorder studies support the use of an atypical antipsychotic and a mood stabilizer as first-line treatment. Antidepressants may also be used to some extent, but data to support this recommendation are needed. Maintenance treatment should probably be a combination of an atypical antipsychotic and a mood stabilizer, although an atypical antipsychotic as monotherapy could also be acceptable. Patients who achieve remission are good candidates for psychoeducation.

Schizoaffective Disorder, Depressive Type

Evidence for this subtype is so limited that this recommendation is based on clinical practice rather than clinical trials. For patients with the depressive type of schizoaffective disorder, the combination of an atypical antipsychotic with an antidepressant or mood stabilizer could be the best treatment. Again, psychoeducation can be provided when the patient achieves remission or some stability.

Electroconvulsive Therapy

Refractory cases of schizoaffective disorder may benefit from electroconvulsive therapy (ECT). Most evidence for efficacy of ECT comes from studies in other disorders. A study³⁶ of response to ECT in patients with bipolar I or II disorder and unipolar depression that was resistant to pharmacologic treatment indicated that ECT was a viable option in these patients. The best outcomes were seen in patients with unipolar depression; residual manic and psychotic symptoms tended to be seen in patients with bipolar I disorder. Another study³⁷ of 8 patients with schizoaffective disorder and 13 patients with depression compared the effectiveness of pharmacotherapy plus ECT as maintenance therapy with pharmacotherapy alone. All patients treated with ECT had longer time to rehospitalization than controls, but the schizoaffective group had poorer outcomes than the depressed group. Clinicians should remember that ECT is an option for patients who do not respond to other treatments.

SUMMARY

The poor diagnostic definition of schizoaffective disorder leads to lack of treatment evidence and inconclusive therapeutic guidelines. Most data come from studies with mixed samples of patients with schizophrenia and schizoaffective

disorder. Currently, the best clinical trial evidence is available for atypical antipsychotics, but lithium and mood stabilizers may have a role, especially in the prevention of relapse. In clinical practice, many patients receive antidepressants, and clinical experience suggests that antidepressants may be required, but more data are needed to support this statement. The best current approach for schizoaffective disorder, bipolar type, is an atypical antipsychotic combined with mood stabilizers or atypical antipsychotic monotherapy. The best approach for schizoaffective disorder, depressive type, is atypical antipsychotics combined with an antidepressant or mood stabilizer. In refractory cases, ECT can be used. Psychoeducation and treatment adherence increase the chance of achieving the best possible outcomes.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), lithium (Lithobid and others), olanzapine (Zyprexa), paliperidone (Invega), risperidone (Risperdal and others), topiramate (Topamax and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, haloperidol, lithium, olanzapine, risperidone, topiramate, and ziprasidone are not approved by the US Food and Drug Administration for the treatment of schizoaffective disorder.

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