

# An Overview of the Treatment of Schizoaffective Disorder

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Schizoaffective disorder is a common, chronic, and frequently disabling psychiatric disorder. However, its pharmacologic treatment has not been well studied. The authors review studies of traditional and novel pharmacologic agents in treatment of schizoaffective disorder, and based on the findings, present preliminary pharmacologic treatment guidelines for the disorder.

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It has long been recognized that there are psychiatrically ill patients who have prominent symptoms of both schizophrenia and mood disorder who do not fit neatly into diagnostic criteria sets for either disorder. Indeed, in his 1919 book *Dementia Praecox and Paraphrenia*,<sup>1</sup> Kraepelin noted that the distinction of dementia praecox from manic-depressive insanity was difficult when there was “a mingling of morbid symptoms of both psychoses.”<sup>1(p261)</sup>

Even though Kasanin introduced the concept of “schizoaffective psychoses” in 1933 to classify those patients who displayed a “blending of schizophrenic and affective symptoms,”<sup>2(p122)</sup> considerable controversy still surrounds the definition, classification, and epidemiology of this condition.<sup>3–10</sup> Operational diagnostic criteria of schizoaffective disorder have varied considerably with respect to the required types and degree of both affective and psychotic symptoms, as well as to the nature of the temporal relationship between affective and psychotic symptoms.<sup>11–14</sup> Regarding classification, the nosologic boundaries between schizoaffective disorder, schizophrenia, and mood disorder remain uncertain. Some authors view schizoaffective disorder as primarily a psychotic disorder (as it is classified in DSM-IV) or a form of schizophrenia, whereas others view it as a variant of mood disorder. Other ways in which the disorder has been viewed is as a heterogeneous mixture of disorders (i.e., the co-occurrence or

dual inheritance of schizophrenia and mood disorder), a distinct disorder separate from schizophrenia and mood disorder, and a disorder that exists on a continuum of psychosis between schizophrenia and mood disorder.<sup>3–10</sup> Finally, epidemiologic data regarding the prevalence of this disorder in the general population are lacking.<sup>15–17</sup>

While controversy over the definition, classification, and epidemiology of schizoaffective disorder continues, several lines of evidence suggest that patients who meet modern diagnostic criteria for the disorder constitute a significant public health problem. First, it has become increasingly apparent that schizoaffective disorder is common in clinical settings. Pooled data<sup>10</sup> from studies that used diagnostic criteria similar to those in DSM-IV yield an estimated mean prevalence of the disorder of 16% ± 12% (range, 1%–19%) in patient populations. Second, 2 studies<sup>12,18</sup> have shown that schizoaffective disorder can be as reliably diagnosed as schizophrenia when operational diagnostic criteria are used. Third, studies of the course and outcome of schizoaffective disorder indicate that it is associated with substantial morbidity and mortality. Specifically, although the long-term outcome of schizoaffective disorder is generally better than that of schizophrenia, it is generally worse than that of mood disorder, with a rate of death by suicide comparable with that of mood disorder.<sup>9</sup>

Despite the seriousness of schizoaffective disorder as a public health problem, the pharmacologic treatment of this disorder has not been well studied—particularly when compared with the systematic study of the pharmacologic treatment of schizophrenia and mood disorder.<sup>10,19–23</sup> In this article, we first review the traditional pharmacologic agents in the acute and maintenance treatment of patients with schizoaffective disorder. We then review available data regarding the new antipsychotics in the treatment of this disorder. We conclude by presenting preliminary psychopharmacologic treatment guidelines for schizoaffective disorder.

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Table 1. Controlled Trials of Lithium, Antidepressants, and Typical Antipsychotics in the Treatment of Schizoaffective Disorder<sup>a</sup>

Study	N	Diagnostic Criteria	Design	Duration (d)	Results
Lithium vs placebo Alexander et al <sup>31</sup>	8	RDC <sup>b</sup>	Lithium vs placebo	28	Lithium > placebo
Antipsychotics vs lithium Johnson et al <sup>24</sup>	14	Mayer-Gross <sup>c</sup>	Chlorpromazine vs lithium	21–28	Chlorpromazine < lithium
Johnson et al <sup>25</sup>	13	Mayer-Gross <sup>b</sup>	Chlorpromazine vs lithium	21	Chlorpromazine = lithium
Shopsin et al <sup>26</sup>	4	DSM-II <sup>b</sup>	Chlorpromazine vs lithium	21	Chlorpromazine > lithium
Prien et al <sup>27</sup>	83	DSM-II <sup>c</sup>	Chlorpromazine vs lithium	21	Chlorpromazine = lithium in mildly active patients; chlorpromazine > lithium in highly active patients
Brockington et al <sup>29</sup>	14	RDC <sup>c</sup>	Chlorpromazine vs lithium	28	Chlorpromazine = lithium
Braden et al <sup>36</sup>	31	RDC <sup>c</sup>	Chlorpromazine vs lithium	28	Chlorpromazine = lithium in mildly active patients; chlorpromazine > lithium in highly active patients
Antipsychotic vs thymoleptic vs combined treatment Brockington et al <sup>29</sup>	36	RDC <sup>d</sup>	Chlorpromazine vs amitriptyline vs chlorpromazine + amitriptyline	28	Poor response to all treatments
Bigelow et al <sup>34</sup>	1	RDC <sup>e</sup>	Acetophenazine vs lithium vs acetophenazine + lithium	100–400	Acetophenazine + lithium > acetophenazine, lithium
Goodnick and Meltzer <sup>37</sup>	30	RDC <sup>e</sup>	Antipsychotic vs lithium vs antipsychotic + lithium	30	Antipsychotic = lithium = antipsychotic + lithium
Thymoleptic vs placebo added to antipsychotic Small et al <sup>28</sup>	8	Feighner <sup>b</sup>	Lithium vs placebo, crossover	28 × 4	Lithium response in mania > depression
Grove et al <sup>32</sup>	2	RDC <sup>e</sup>	Lithium vs placebo, crossover	28 × 4	Not specified
Prusoff et al <sup>33</sup>	35	DSM-II <sup>d</sup>	Amitriptyline vs placebo	120	Amitriptyline > placebo for depression but < placebo for thought disorder
Biederman et al <sup>30</sup>	36	RDC <sup>b</sup>	Lithium vs placebo	35	Lithium > placebo
Carman et al <sup>35</sup>	7	RDC <sup>b</sup>	Lithium vs placebo, crossover	28 × 3	Lithium > placebo

<sup>a</sup>Adapted from reference 10.

<sup>b</sup>Patients included both bipolar and depressive subtypes.

<sup>c</sup>Patients included bipolar (manic subtype) only.

<sup>d</sup>Patients included depressive subtype only.

<sup>e</sup>Subtypes not specified.

## PREVIOUS PHARMACOLOGIC TREATMENT STUDIES AND STRATEGIES

Only 14 controlled studies<sup>24–37</sup> have examined standard antipsychotics, lithium, or antidepressants in the acute treatment of patients with schizoaffective disorder (reviewed in reference 10; see Table 1). Several impressions emerge from these studies. First, the total number of patients with schizoaffective disorder studied in these controlled treatment trials is small (N = 322). Second, the patients studied in these trials cannot be pooled for analysis because of differences in operational diagnostic criteria used to define the disorder and in study design and duration. Specifically, none of these 14 studies used modern diagnostic criteria to define schizoaffective disorder. Indeed, the most recent of these studies was published in 1984.<sup>37</sup> In addition, the 3 major study designs were comparison of lithium versus an antipsychotic, comparison of an antipsychotic versus a thymoleptic (lithium or an antidepressant) versus combined treatment, and comparison of a thymoleptic versus placebo added to ongoing antipsychotic treatment.

As shown in Table 1, 8 studies compared lithium with standard antipsychotic agents.<sup>24–27,29,34,36,37</sup> In general, typical antipsychotics and lithium were comparable in effi-

cacy, except in agitated or highly active patients. In this patient subtype, antipsychotics were superior to lithium. Of note, 2 of these studies<sup>34,37</sup> also compared lithium and antipsychotic monotherapy with lithium-antipsychotic combination treatment. In the first, Bigelow et al.<sup>34</sup> reported a longitudinal controlled comparison trial of lithium, acetophenazine, and the combination in a single subject who responded only to the combination. In the second, Goodnick and Meltzer<sup>37</sup> compared the response of 30 patients to treatment with lithium alone, an antipsychotic alone, or the combination and found no differences in the degree of improvement in either mood or psychotic symptoms across treatment groups.

Four of these controlled studies<sup>28,30,32,35</sup> compared the addition of lithium versus placebo to ongoing treatment with a standard antipsychotic. In 3 of these studies<sup>28,30,35</sup> (all of which used modern diagnostic criteria for schizoaffective disorder), the addition of lithium was superior to that of placebo. This finding provides support to the common clinical practice of combination treatment with a mood stabilizer and a typical antipsychotic for the patient with the bipolar type of schizoaffective disorder.

Only 2 of these controlled studies<sup>29,33</sup> assessed the acute treatment of schizoaffective disorder, depressive type. In

**Table 2. Controlled Studies of Typical Antipsychotics, Lithium, and Combined Treatment as Maintenance Therapy in Schizoaffective Disorder<sup>a</sup>**

Study	N	Diagnostic Criteria	Design	Duration (mo)	Results
Angst et al <sup>45</sup>	44	WHO	Lithium vs imipramine	up to 36	Lithium > imipramine
Prien et al <sup>46</sup>	6	DSM-II	Lithium vs placebo	up to 24	60% relapse on lithium
Mattes and Nayak <sup>47</sup>	14	RDC	Fluphenazine vs lithium	up to 12	Lithium: all relapsed or required fluphenazine; fluphenazine: 57% response

<sup>a</sup>Adapted from reference 10.

the first,<sup>29</sup> combined treatment with amitriptyline and chlorpromazine was found not to be superior to treatment with either drug alone. In the second,<sup>33</sup> amitriptyline was superior to placebo for depression, but inferior to placebo for thought disorder, when added to ongoing antipsychotic therapy. Despite the findings of these studies, combination treatment with an antidepressant and a typical antipsychotic has become a common clinical strategy for the patient with the depressive subtype of schizoaffective disorder.

## TYPES OF TREATMENT IN SCHIZOAFFECTIVE DISORDER

### Antiepileptic Mood Stabilizers

Data primarily from open trials suggest that valproate and carbamazepine, administered alone or in combination with typical antipsychotics, may be effective in reducing manic and psychotic symptoms in some patients with schizoaffective disorder, both acutely and over the long term.<sup>38-40</sup> However, of the 2 controlled studies<sup>41,42</sup> of carbamazepine in the treatment of schizoaffective disorder, 1<sup>41</sup> found only modest benefit when the drug was added to ongoing antipsychotic treatment. The second<sup>42</sup> found a trend toward greater improvement with lithium than with carbamazepine in a group of patients with bipolar and schizoaffective disorders. Response in this study, however, was not separated by diagnosis. Although controlled trials of valproate in schizoaffective disorder have not been conducted, the successful use of valproate in combination with clozapine in patients with schizoaffective disorder has been reported.<sup>43,44</sup>

### Maintenance Treatment

Only 3 controlled studies<sup>45-47</sup> have assessed the efficacy of lithium (N = 32), typical antipsychotics (N = 7), or imipramine (N = 22) in the maintenance treatment of schizoaffective disorder (see Table 2). In the first, Angst et al.<sup>45</sup> found lithium to be significantly more effective than imipramine in preventing recurrent mood and psychotic epi-

sodes. In the other 2 studies,<sup>46,47</sup> lithium alone was ineffective in preventing recurrent mood and psychotic episodes. In the only maintenance study<sup>47</sup> comparing lithium with an antipsychotic, the potential superiority of antipsychotic treatment was not established because of the small sample size. Common maintenance strategies in clinical practice include the combination of a typical antipsychotic with one or more thymoleptics (e.g., an antipsychotic with lithium, valproate, and/or carbamazepine for patients with the bipolar subtype, and an antipsychotic with an antidepressant for patients with the depressive subtype). However, these strategies have not been fully evaluated in controlled trials.<sup>21</sup>

### New (Atypical) Antipsychotics

Clozapine, the first atypical antipsychotic drug, has been available for use in the United States since 1990. In addition to its efficacy in positive and negative psychotic symptoms in schizophrenia (including in treatment-refractory patients),<sup>48</sup> preliminary evidence also suggests that clozapine may ameliorate affective, especially manic, symptoms.<sup>49-52</sup> As shown in Table 3, 6 studies<sup>49,53-57</sup> (5 open and 1 controlled) have examined the efficacy of clozapine in the treatment of patients with schizoaffective disorder. Pooling data from those trials that compared clozapine response between patients with schizophrenia and those with schizoaffective disorder, patients with schizoaffective disorder showed higher response rates (pooled mean  $\pm$  SD, 74%  $\pm$  15%) than patients with schizophrenia (pooled mean  $\pm$  SD, 52%  $\pm$  9%).<sup>10,23</sup> These findings, however, must be regarded as preliminary, since only 1 of these studies<sup>56</sup> was a double-blind, randomized, controlled trial. Also, clozapine was not administered as monotherapy in many cases.

The efficacy of risperidone in the treatment of patients with schizoaffective disorder has been evaluated in 5 open studies<sup>58-62</sup> and 1 controlled trial<sup>63</sup> (see Table 3). In these studies, risperidone was reported to be effective in depressive, manic, and psychotic symptoms in patients with both the bipolar and depressive subtypes. However in 2 of these studies,<sup>59,62</sup> patients with the bipolar subtype of the disorder displayed exacerbations of or switches into hypomania or mania with risperidone treatment. Also, in the only controlled study, Ceskova and Svestka<sup>63</sup> compared the antipsychotic and thymoleptic effects of risperidone (2-20 mg/day) with haloperidol (2-20 mg/day) in an 8-week, double-blind, randomized trial in 49 patients with schizophrenia and 13 patients with schizoaffective disorder (3 with manic symptoms and 10 with depressive symptoms). None of the patients with manic symptoms was randomly assigned to risperidone, and a separate analysis of response in the patients with schizoaffective disorder was not reported. Nonetheless, the authors' impressions were that risperidone did not differ from haloperidol in reducing depressive or anxious symptoms.

Table 3. Studies of Clozapine and Risperidone in Schizoaffective Disorder<sup>a</sup>

Study	N	Design	Duration	Results
<b>Clozapine</b>				
Lindström <sup>53</sup>	7	Open	Up to 12 y	Not specified
Naber and Hippus <sup>54</sup>	60	Open	Up to 4.3 y	65% schizoaffective, moderate/marked response
Stefanowicz <sup>55</sup>	10	Open	Up to 1 mo	10/10 moderate/marked response
McElroy et al <sup>49</sup>	25	Open	Up to 14 y	85% schizoaffective, bipolar type; 100% schizoaffective, depressive type; moderate/marked response
Banov et al <sup>57</sup>	81	Open	Mean 1.5 y	70% schizoaffective, bipolar type; 50% schizoaffective, depressive type; moderate/marked response
Malhotra et al <sup>56</sup>	11	Double-blind, clozapine vs placebo	4 wk	36% moderate/marked response
<b>Risperidone</b>				
Hillert et al <sup>58</sup>	3	Open	6 wk	3/3; moderate/marked response
Ceskova and Svestka <sup>63</sup>	13	Double-blind, risperidone vs haloperidol	8 wk	Risperidone = haloperidol
Dwight et al <sup>59</sup>	8	Open	Up to 8 wk	Possible antidepressant effects
Keck et al <sup>60</sup>	81	Open	Up to 24 wk	56% schizoaffective, bipolar type; 87% schizoaffective, depressive type; moderate/marked response
Madhusoodanan et al <sup>61</sup>	3	Open	Up to 4 wk	2/3 moderate/marked response
Sajatovic et al <sup>62</sup>	1	Open	4 wk	1/1 moderate/marked response

<sup>a</sup>Adapted from reference 10.

The structural and pharmacologic similarities between clozapine and olanzapine raise the possibility that olanzapine may have thymoleptic properties similar to those of clozapine.<sup>64</sup> Indeed, controlled studies have shown that olanzapine is superior to haloperidol in alleviating negative and depressive symptoms in schizophrenia,<sup>65,66</sup> and superior to placebo in reducing manic and psychotic symptoms in acute mania associated with bipolar I disorder.<sup>67</sup> To date, 1 controlled study<sup>65</sup> has compared the efficacy of olanzapine (5–20 mg/day) with haloperidol (5–20 mg/day) in 300 patients with schizoaffective disorder (and is therefore the largest controlled trial ever conducted in schizoaffective disorder). In this study, schizoaffective patients, in general, and those with the bipolar subtype who received olanzapine displayed statistically significantly greater improvement in Brief Psychiatric Rating Scale total, Positive and Negative Syndrome Scale (PANSS) total, PANSS negative, Clinical Global Impressions (CGI)-Severity of Illness scale, and Montgomery-Asberg Depression Rating Scale total scores compared with patients who received haloperidol ( $p < .01$  for all schizoaffective patients;  $p < .05$  for schizoaffective, bipolar type patients). In the depressive subgroup, the mean improvement in these same variables was also significantly greater in olanzapine-treated patients than in haloperidol-treated patients, but the magnitude of this difference was less robust than in the bipolar subgroup.

Sertindole, an atypical antipsychotic not available for clinical use in the United States, has been examined in the treatment of patients with schizoaffective disorder in one open-label, long-term study.<sup>68</sup> Of 402 schizoaffective patients who received sertindole in this study, 281 (70%) also received concurrent treatment with divalproex for affective symptoms. Sertindole, alone or in combination

with divalproex, produced an overall reduction in the CGI of  $> 2$  by 2 months of treatment. For the majority of patients, this response was sustained throughout the 1-year follow-up period. However, because of the thymoleptic activity of divalproex, the potential thymoleptic properties of sertindole could not be separately assessed in this study. Further data are therefore needed to assess the potential thymoleptic properties of this atypical antipsychotic.

### CONCLUSIONS AND PRELIMINARY GENERAL TREATMENT GUIDELINES

Schizoaffective disorder is a common, chronic, and frequently disabling psychiatric condition. Clinical experience indicates that patients with this disorder usually require complex psychopharmacologic treatment regimens for optimal outcomes. Yet the systematic study of the medical treatment of this disorder has been relatively neglected. Indeed, the pharmacologic treatment of schizoaffective disorder has been based on limited data from trials of thymoleptics, typical antipsychotics and, more recently, new antipsychotics in patients with the disorder defined by various criteria; extrapolation from clinical trials of patients with schizophrenia and mood disorders; and assumptions (which may or may not be accurate) that the bipolar subtype of schizoaffective disorder is closely related to bipolar disorder, whereas the depressive subtype is related to schizophrenia or psychotic depression.<sup>16</sup>

Nonetheless, several preliminary guidelines for the treatment of schizoaffective disorder based on available knowledge may be proposed. One general guideline is that both affective and psychotic symptoms should be considered of equal importance in the evaluation and treatment of this disorder. In other words, both sets of target symp-

toms should be evaluated at baseline and at regular intervals as the patient progresses in treatment. This careful evaluation includes precisely identifying the mood and psychotic symptoms and the temporal relationship between them. Thus, with respect to mood symptoms, it is very important to subtype the schizoaffective disorder into bipolar versus depressive types. If a bipolar type exists or is suspected, it is extremely important to assess for mixed and rapid-cycling states, including those not clearly defined in DSM-IV, such as major depression or dysthymia with hypomanic features (e.g., so-called mixed depression). It is also important to evaluate and treat subthreshold affective and psychotic symptoms, including interepisode symptoms, such as dysthymic, hypomanic, and cyclothymic symptoms and referential, paranoid, and grandiose ideation.

A second general guideline is that most patients will need to be treated with agents that have antipsychotic and thymoleptic properties. If standard antipsychotics are used, available data, which are limited, suggest that these agents will often need to be combined with mood stabilizers and/or antidepressants for optimal results. Preliminary results suggest that the atypical antipsychotics have thymoleptic profiles that differ from those of the standard antipsychotics (and possibly from one another) with the potential for greater efficacy in both subtypes of schizoaffective disorder. The better side effect and safety profile of the new atypical antipsychotics, along with data suggesting their efficacy in depressive (olanzapine, risperidone) and manic (olanzapine) symptoms, suggests that these agents might be ideal first-line treatment for patients with schizoaffective disorder. Whether these agents provide adequate monotherapy treatment for schizoaffective disorder, however, needs to be assessed in controlled comparison trials. Nonetheless, preliminary clinical experience indicates that mood stabilizers and antidepressants can be successfully and safely added to atypical antipsychotics for residual manic and depressive symptoms, respectively.

Thus, pharmacologic treatment strategies for the depressive type of schizoaffective disorder would include novel antipsychotic monotherapies, novel antipsychotic/antidepressant combinations, standard antipsychotic/antidepressant combinations, and any of the above in combination with a mood stabilizer for patients with treatment resistance and/or bipolar features (e.g., a family history of bipolar disorder or subthreshold hypomanic symptoms). Pharmacologic treatment strategies for the bipolar type of schizoaffective disorder would include novel antipsychotic monotherapies (especially with olanzapine or clozapine), novel antipsychotic/mood-stabilizer combinations (e.g., olanzapine or clozapine with lithium or valproate), conventional antipsychotic/mood-stabilizer combinations, and any of the above in combination with an antidepressant for patients with persistent depression (e.g., olanzapine, valproate, and a serotonin reuptake inhibitor or bupropion).

In conclusion, the pharmacologic treatment of schizoaffective disorder, a common, chronic, and frequently disabling psychiatric illness, has been the subject of few modern pharmacologic treatment studies. Nonetheless, available data supports the combined use antipsychotics (standard and novel) with thymoleptics (mood stabilizers and/or antidepressants) and possibly monotherapy with novel antipsychotics in the treatment of this disorder. Further studies evaluating the efficacy of novel agents in this disorder, including new antipsychotics, antiepileptic mood stabilizers, and new antidepressants, are needed.

*Drug names:* acetophenazine (Tindal), amitriptyline (Elavil and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), olanzapine (Zyprexa), risperidone (Risperdal).

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#### DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for schizoaffective disorder: carbamazepine, valproate, and lithium.