Differential Diagnosis and Medical Management of Schizoaffective Disorder

A DELPHI-BASED RESOURCE

DSM-IV TR Criteria for Schizoaffective Disorder (SAD)\(^a\)

- An uninterrupted period of illness during which there is a major depressive episode, a manic episode, or a mixed episode, concurrent with symptoms that meet criterion A for schizophrenia\(^b\)
- During the same period of illness, delusions or hallucinations persisting for >2 weeks in the absence of prominent mood symptoms
- Symptoms meeting criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness
- The disturbance is not due to the direct physiological effects of a drug of abuse, a medication, or a general medical condition
- Bipolar subtype: if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes)
- Depressive subtype: if the disturbance includes only a major depressive episode

\(^{a}\)DSM-IV TR diagnostic criteria are not consistent with ICD–10 criteria, and genetic, neurophysiologic, and psychological benchmarks of schizoaffective disorder are not unequivocal.\(^{1,2}\)

\(^{b}\)Includes delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Does not include symptoms due to a general medical condition.\(^{3}\)

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SAD Treatment Algorithm

SAD constitutes a heterogeneous clinical construct encompassing both schizophrenia and mood disorders and forming a continuum between the 2 conditions. DSM-IV TR defines SAD as a longitudinal, uninterrupted disorder but ICD-10 classes it as episodic. Nevertheless, it is generally agreed that duration, and relative proportion of psychotic vs affective symptoms can enable accurate SAD diagnosis and treatment optimization. To date, treatment of SAD is largely symptomatic and predicated on the management of other psychotic and/or mood disorders. This algorithm summarizes best-practice parameters derived from the literature.

Assessment and Diagnosis

- Determine whether patient meets criteria for SAD
  - Conduct diagnostic interview
  - Obtain history and self-report, including current medications
  - Use structured diagnostic questionnaires and rating scales such as Hamilton Depression Rating Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), Positive and Negative Syndrome Scale (PANSS), Personal and Social Performance (PSP) scale, Young Mania Rating Scale (YMRS)
- Obtain physical exam and laboratory panel
- Rule out symptoms secondary to a substance-induced or general medical condition
- Assess psychiatric and physical comorbidities (eg, anxiety disorder, migraine, substance-use disorder, Axis II disorder, metabolic syndrome)
- Evaluate need for and components of multimodal treatment plan

The selection of medications used to treat SAD depends on whether the depressive or bipolar subtype is present. When there is good premorbid function, early treatment frequently improves outcomes. In the depressive subtype, an antipsychotic is used sometimes in combination with an antidepressant. In the bipolar subtype, an antipsychotic can be used in combination with a mood stabilizer. When psychosis is not prominent, psychotherapy can be very effective.

Circled numbers in this flow chart are expanded upon in the corresponding numbered boxes. Assessment and diagnostic recommendations run from top down in this schematic.
1. **SAD with prominent psychotic component**
   - Assess proportionality of depressive vs bipolar components

2. **SAD with minimal psychotic component**
   - Assess proportionality of depressive vs bipolar components

3. **SAD with prominent psychotic component—bipolar**
   - Initiate immediate antipsychotic pharmacotherapy
   - Assess probable need for and responsiveness to mood stabilizers
   - Consider addressing manic elements with mood stabilizer
   - Initiate psychotherapy tailored to patient and family needs

4. **SAD with prominent psychotic component—depressive**
   - Initiate immediate antipsychotic pharmacotherapy
   - Assess probable need for and responsiveness to an antidepressant
   - Initiate psychotherapy tailored to patient and family needs

5. **SAD with minimal psychotic component—bipolar**
   - Assess pharmacotherapeutic approach to treating psychotic component
   - Consider mood-stabilizing pharmacotherapy
   - Enhance patient insight into the illness; include family, friends, partners, and caregivers
   - Teach appropriate social skills, focusing on vocational functioning
   - Use cognitive behavioral therapy to help patients understand relationships between feelings, thinking patterns, and distress
   - Consider behavioral tailoring to help develop a routine for taking medication
   - Educate patients about treatment and the illness (eg, psychoeducation focused on medication effects, timing of dosing, etc)

6. **SAD with minimal psychotic component—depressive**
   - Assess pharmacotherapeutic approach to treating psychotic component
   - Consider antidepressant pharmacotherapy
   - Assess current quality of life and use cognitive behavioral therapy to help patients understand relationship between feelings, thinking patterns, and distress
   - Address social/vocational functioning with individual/family counseling

Need for adjunctive antidepressants or mood stabilizers is not universally agreed upon, given the mood-stabilizing properties of the newest generation antipsychotic medications.
SAD Diagnosis and Treatment Quick Reference

Phenomenology

- Symptoms that meet criterion A for schizophrenia (delusions, hallucinations, disordered thoughts/speech or behavior, or negative symptoms) concurrent with significant manic or depressive symptoms
- Delusions, hallucinations, or disordered thoughts without significant manic/depressive symptoms persisting for >2 weeks
- Manic or depressive phase duration significant in comparison to total duration of psychotic illness
- Two subtypes: SAD with bipolar symptoms and SAD with depressive symptoms, with latter more prevalent with increasing age of patient population
- Clinical studies reporting pharmacotherapeutic success in SAD are limited

Etiology/Pathophysiology

- Risk factors include female sex and familial/genetic predisposition to psychosis and mood disorders
- Neuroanatomic abnormalities likely present in striatum, corpus callosum, and neocortical volume
- Neurophysiologic abnormalities likely present in signal processing, cognitive impairment (e.g., memory and executive functions), saccadic eye movements, and altered evoked potentials, which mirror bipolar disorder and schizophrenia

Assessment and Differential Diagnosis

- Monitor symptoms longitudinally to ensure optimal assessment and treatment response
- Perform physical exam, laboratory panel, medical/psychiatric history, and assessment of comorbidities (e.g., obesity, diabetes, anxiety, substance-induced syndromes)
- Inquire about suicidal/homicidal ideation, evidence of self-neglect/disability, and any history of admission to inpatient psychiatric facilities
- Use rating scales including HAM-D, MADRS, PANSS, PSP, and YMRS, to quantify affective/psychiatric symptoms

Initial Treatment

- Utilize a multimodal approach, combining pharmacotherapy with psychotherapy and psychosocial/vocational intervention, such as individual and family counseling
- Combine ≥1 psychotropic drugs (an antipsychotic with a mood-stabilizing or antidepressant medication) based on SAD subtype, medical/psychiatric comorbidities, and psychosocial variables, including medication adherence
- Initiate antipsychotic therapy with an atypical agent first in SAD with bipolar symptoms; subsequently add a mood stabilizer if needed
- Initiate antipsychotic therapy first in SAD with depressive symptoms, to limit frequency/severity of psychoses. After stabilization of psychosis, antidepressant therapy should be considered

Ongoing Care

- Assess antipsychotic and mood-stabilizer pharmacotherapy for early nonresponse (<20% PANSS reduction) and adjust treatment plan accordingly
- Continue pharmacotherapy in partial responders for 8-12 weeks with dose optimization to determine efficacy
- Monitor for changes in the balance between psychotic symptoms and affective/mood symptoms. Initial SAD subtype diagnosis is frequently unstable and may progress to schizophrenia or major depression/mania with psychotic features
- Watch for rapid switch from depression to mania and/or a mixed state after treatment with an antidepressant; may suggest SAD with bipolar symptoms
- Initiate other therapeutic options, such as electroconvulsive therapy or clozapine if patient is consistently unresponsive to multiple pharmacotherapy trials or other targeted, individualized interventions
## Select Pharmacologic Interventions for SAD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relevant Indications</th>
<th>Boxed Warnings</th>
<th>Side Effect Profile</th>
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<tr>
<td><strong>Typical Antipsychotics</strong></td>
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| Fluphenazine | • Prolonged and parenteral therapy for schizophrenia  
• Available as oral, injectable, and long-acting injectable formulations | 1 | Akathisia, tardive dyskinesia, Rabbit syndrome, extrapyramidal symptoms (EPS), neuroleptic malignant syndrome, and, rarely, hypothermia and blood pressure fluctuations  
**Note:** Depot fluphenazine injections used in cases of poor compliance |
| Haloperidol | • Schizophrenia  
• Severe behavioral problems in children  
• Available as oral, injectable, and long-acting injectable formulations | 1 | Tardive dyskinesia, akathisia, acute dystonia, EPS, and neuroleptic malignant syndrome  
**Note:** Depot haloperidol injections used in cases of poor compliance |
| **Atypical Antipsychotics** | | | |
| Aripiprazole | • Schizophrenia  
• Manic/mixed episodes associated with bipolar I disorder (BD I), adjunctive with lithium or valproate  
• Maintenance treatment of BD I  
• Major depressive disorder (adjunctive)  
• Agitation associated with schizophrenia or BD I  
• Available as oral and injectable formulations | 1,2 | Akathisia, EPS, sedation, restlessness, and tremor |
| Asenapine | • Acute treatment of schizophrenia  
• Acute treatment of mixed or manic episodes associated with BD I, with or without psychotic features  
• Available as an oral formulation | 1 | Somnolence, insomnia, EPS, headache, akathisia, and dizziness |
| Clozapine | • Treatment-resistant schizophrenia  
• Reducing the risk of recurrent suicidal behavior in patients with schizophrenia or SAD  
• Available as an oral formulation | 3 | Neuroleptic malignant syndrome, weight gain, hyperlipidemia, hyperglycemia, anticholinergic effects, and cognitive/motor impairment |
| Iloperidone | • Acute treatment of schizophrenia  
• Available as an oral formulation | 1 | Hypotension, dizziness, somnolence, tachycardia, and QTc prolongation |
| Olanzapine | • Schizophrenia  
• Acute or mixed mania episodes associated with BD I  
• Maintenance treatment of BD I  
• Acute agitation in patients with schizophrenia or bipolar mania  
• Depressive episodes associated with BD I (in conjunction with fluoxetine)  
• Treatment-resistant depression (in conjunction with fluoxetine)  
• Available as oral and long-acting injectable formulations | 1 | Neuroleptic malignant syndrome, weight gain, hyperglycemia, hyperlipidemia, and suicidality |

*Continued*
### Differential Diagnosis and Medical Management of **SCHIZOAFFECTIVE DISORDER**

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<tbody>
<tr>
<td>Paliperidone</td>
<td>• SAD (Note: only medication currently approved for SAD)</td>
<td>1</td>
<td>Neuroleptic malignant syndrome, QTc prolongation, tardive dyskinesia, and hyperprolactinemia</td>
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<tr>
<td></td>
<td>• Acute and/or maintenance treatment of patients with schizophrenia</td>
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<td></td>
<td>• Available as extended-release oral and long-acting injectable formulations</td>
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<tr>
<td>Quetiapine</td>
<td>• Schizophrenia</td>
<td>1,2</td>
<td>Somnolence, dizziness, dry mouth, constipation, and weight gain</td>
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<td></td>
<td>• Acute treatment of manic episodes associated with BD I, both as monotherapy and as an adjunct to lithium or divalproex</td>
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<tr>
<td></td>
<td>• Acute treatment of depressive episodes associated with bipolar disorder</td>
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<td></td>
<td>• Maintenance treatment of BD I</td>
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<td></td>
<td>• Available as oral and extended-release oral formulations</td>
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<tr>
<td>Risperidone</td>
<td>• Schizophrenia</td>
<td>1</td>
<td>Cerebrovascular events in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, and hyperprolactinemia</td>
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<tr>
<td></td>
<td>• Acute mania or mixed episodes associated with BD I</td>
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<td>• Maintenance treatment of BD I</td>
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<td></td>
<td>• Available as oral and long-acting injectable formulations</td>
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<tr>
<td>Ziprasidone</td>
<td>• Schizophrenia</td>
<td>1</td>
<td>QTc prolongation, neuroleptic malignant syndrome, tardive dyskinesia, and rash</td>
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<td></td>
<td>• Acute manic or mixed episodes associated with BD I</td>
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<td>• Maintenance treatment of BD I</td>
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<td></td>
<td>• Available as oral and injectable formulations</td>
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### Adjunctive Medications

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<tr>
<td>Bupropion</td>
<td>• Major depressive disorder</td>
<td>Agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, and tremor</td>
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<td>Note: Frequently used for bipolar-prominent SAD cases</td>
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<tr>
<td>Carbamazepine</td>
<td>• Acute manic and mixed episodes associated with BD I</td>
<td>Drowsiness, headache, motor coordination impairment, and upset stomach</td>
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<td><strong>Note:</strong> Frequently used for bipolar-prominent SAD cases</td>
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<tr>
<td>Desipramine</td>
<td>• Depression</td>
<td>Dry mouth, anorexia, sedation, constipation, and increased appetite</td>
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<td><strong>Note:</strong> Side effect incidence is reduced compared with first-generation tricyclic antidepressants</td>
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<tr>
<td>Divalproex/Valproic Acid</td>
<td>• Acute manic and mixed episodes associated with bipolar disorder</td>
<td>Drowsiness, headache, dizziness, motor coordination impairment, upset stomach, liver enzyme elevation, thrombocytopenia, hair loss, and possible teratogenicity during pregnancy</td>
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<tr>
<td>Duloxetine</td>
<td>• Major depressive disorder</td>
<td>Nausea, somnolence, dry mouth, headache, and dizziness</td>
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<td>• Generalized anxiety disorder</td>
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<tr>
<td>Fluoxetine</td>
<td>• Major depressive disorder</td>
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<td></td>
<td>• Obsessive-compulsive disorder</td>
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<td>• Panic disorder</td>
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<tr>
<td>Fluvoxamine</td>
<td>• Obsessive-compulsive disorder</td>
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<td>• Social anxiety disorder</td>
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<tr>
<td>Imipramine</td>
<td>• Symptoms of depression</td>
<td>2</td>
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<td>Lamotrigine</td>
<td>• Maintenance treatment of BD I</td>
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<tr>
<td>Lithium carbonate</td>
<td>• Acute manic episodes associated with bipolar disorder</td>
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<td></td>
<td>• Maintenance treatment of bipolar disorder</td>
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<tr>
<td>Mirtazapine</td>
<td>• Major depressive disorder</td>
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<tr>
<td>Paroxetine</td>
<td>• Major depressive disorder</td>
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<td>• Generalized anxiety disorder</td>
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<tr>
<td>Sertraline</td>
<td>• Major depressive disorder</td>
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<td></td>
<td>• Social anxiety disorder</td>
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<tr>
<td>Tranylcypromine</td>
<td>• Major depressive episode without melancholia</td>
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<tr>
<td>Venlafaxine</td>
<td>• Major depressive disorder</td>
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<td>• Generalized anxiety disorder</td>
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<td>• Social anxiety disorder</td>
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<td>• Panic disorder</td>
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Complete prescribing information is available at PSYCHClinician.com

**Boxed Warnings**

1. Increased mortality in elderly patients with dementia-related psychosis.  
2. Increased risk of suicidality in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders.  
3. Agranulocytosis, seizures, myocarditis, and cardiovascular/respiratory adverse events, especially in elderly patients with dementia-related psychoses.  
4. Serious dermatologic reactions including Stevens-Johnson syndrome, HLA-B1502 allele, aplastic anemia, and agranulocytosis.  
5. Hepatotoxicity and hepatic failure resulting in fatalities. Valproate can produce teratogenic effects, such as neural tube defects, in a developing fetus. Cases of life-threatening pancreatitis have been reported in both children and adults.  
6. Life-threatening serious rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death. The rate of serious rash is higher in pediatric patients than in adults.  
7. Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels.

Drs. Christoph Correll, Joseph Goldberg and Henry Nasrallah selected the screening tools, medications and related information for this educational resource.
References


This resource is part of an educational program, components of which include:

- **Annals of Clinical Psychiatry**, Vol 22. No 4, November 2010
- Additional resources made available at PSYCHClinician.com