Understanding Schizoaffective Disorder: From Psychobiology to Psychosocial Functioning

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Psychobiologic evidence and psychosocial functioning in patients with schizoaffective disorder suggest that the disease may be a distinct disorder, a variant of schizophrenia or affective disorders, the comorbidity of schizophrenia and a mood disorder, or an intermediate disorder on a spectrum that ranges from schizophrenia to mood disorders. These data, although inconclusive, contribute to clinicians' understanding of the etiology of the disorder. Further research may lead to an increased understanding of the disorder, improved treatment, and, ultimately, better outcomes.

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The understanding of the relationship between schizoaffective disorder, schizophrenia, and affective disorders is changing as a result of psychobiologic and psychosocial evidence. Genetic, neuroimaging, electrophysiologic, neuroendocrinologic, neurochemical, and neurocognitive data, as well as measures of psychosocial functioning, suggest several models for a classification of these disorders. Schizoaffective disorder may be a unique psychiatric disorder, a variant of schizophrenia or bipolar disorder, the comorbidity of schizophrenia and bipolar disorder or major depression, or an intermediate condition on a spectrum of psychosis between schizophrenia and mood disorders.[1]

A recent review[1] examined demographic, family, biologic, symptomatic, and clinical variables among patients with schizophrenia, schizoaffective disorder, and mood disorders. Regarding each variable, schizoaffective disorder was intermediate between the other disorders, sometimes being more similar to schizophrenia and sometimes being more similar to mood disorders; Table 1 shows selected results.

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PSYCHOBIOLOGY OF SCHIZOAFFECTIVE DISORDER

Biologic-Genetic Models

Several models of the biologic-genetic relationship between schizophrenia, schizoaffective disorder, and mood disorders have been proposed, but genetic evidence suggests that some models can be rejected.[2]

A unidimensional model of clinical phenotypes uses Venn diagrams to show 6 possible levels of etiologic overlap (Figure 1A): (1) no overlap exists per se because all psychotic and mood disorders are actually elements of a single unstructured psychosis, for which risk is influenced by many genes with no degree of specificity; (2) 2 distinct disease processes exist for prototypical schizophrenia and prototypical bipolar disorder, and their genes and associated proteins and biologic pathways do not overlap; (3) 2 distinct disease processes exist but their etiologies overlap; (4) 3 distinct disease processes exist and overlap; (5) multiple distinct disease processes exist and overlap; or (6) a structured continuum of psychosis between nonaffective and affective disorder categories exists.[2] The first 2 possible relationships between disorders have been invalidated by data showing some genetic specificity of risk for prototypical schizophrenia and prototypical bipolar disorder as well as some phenotypic overlap. The other 4 theories cannot be ruled out, but insufficient evidence is available to delineate particular disease processes.

Second, the clinical-functional model of psychosis, like the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (*DSM-IV*),[3] places schizophrenia and mood disorders at opposite poles of a spectrum (Figure 1B).[2] In the *DSM-IV*, schizoaffective disorder occupies a central position. However, the proposed alternative model would have fewer restrictions than *DSM-IV* places on schizoaffective disorder, thus including a larger proportion of patients with prominent psychotic and affective symptoms. This intermediate area of mixed psychoses would therefore encompass several current diagnostic categories.

For Clinical Use

- Several models of the biologic-genetic relationship between schizoaffective disorder, schizophrenia, and mood disorders have been proposed.
- Some biologic-genetic abnormalities are shared between these disorders and others are more specific to particular symptoms and syndromes.
- Neurobiologic and psychosocial functioning data suggest that schizoaffective disorder occupies an intermediate position between schizophrenia and affective disorders.
- Negative symptoms and cognitive dysfunction in psychotic patients especially need to be addressed, as these symptoms adversely affect psychosocial functioning.

The third model is a 3-dimensional representation of the psychopathology domains of psychosis, mania, and depression (Figure 1C).[2] Current diagnostic categories can be mapped to different areas of the dimensional planes. Additional dimensions may be needed for other domains of clinical characteristics and psychological functioning so that biologically relevant clinical variations can be captured.

The review of these potential nosologic classifications makes clear that biologic, endophenotypic, epidemiologic, and treatment response data are sorely needed to aid an evidence-based delineation between specific and meaningfully differentiated disease entities within the spectrum of psychotic and mood manifestations. What follows is a review of the currently available data that can help inform such decisions and that will guide further research efforts.

Genetics

Some genetic studies have found overlaps between schizophrenia, schizoaffective disorder, and mood disorders, while others have not. A review of studies[4] focusing on the genetic architecture of schizophrenia and bipolar I disorder yielded conflicting results.

Studies[5,6] of first-degree family members have found indications of genetic overlap and cosegregation, ie, the tendency for closely linked genes and genetic markers to be inherited together. For example, in a Swedish study,[5] relatives of individuals with schizophrenia or bipolar disorder were found to be at increased risk for one or both of these disorders, suggesting a common genetic cause. Similarly, a Spanish study[6] of psychotic inpatients and their relatives found that, regardless of the proband's diagnosis, family members were at increased risk for schizophrenia and mood disorders.

Conversely, some studies[7–9] have supported genetic demarcation. For instance, a study[7] of twins suggested that, while some genetic risk factors for schizophrenic and manic syndromes were shared, other genetic contributions to these 2 disorders were syndrome-specific. However, several of the genetic risk factors for schizoaffective syndromes were entirely shared in common with schizophrenic and manic syndromes, supporting the view that schizoaffective disorder is an intermediary genophenotype between schizophrenia and mood disorders.

Table 1. Summary of Studies of the Biologic-Genetic Overlap Between Schizoaffective Disorder, Schizophrenia, and Mood Disorders[a]

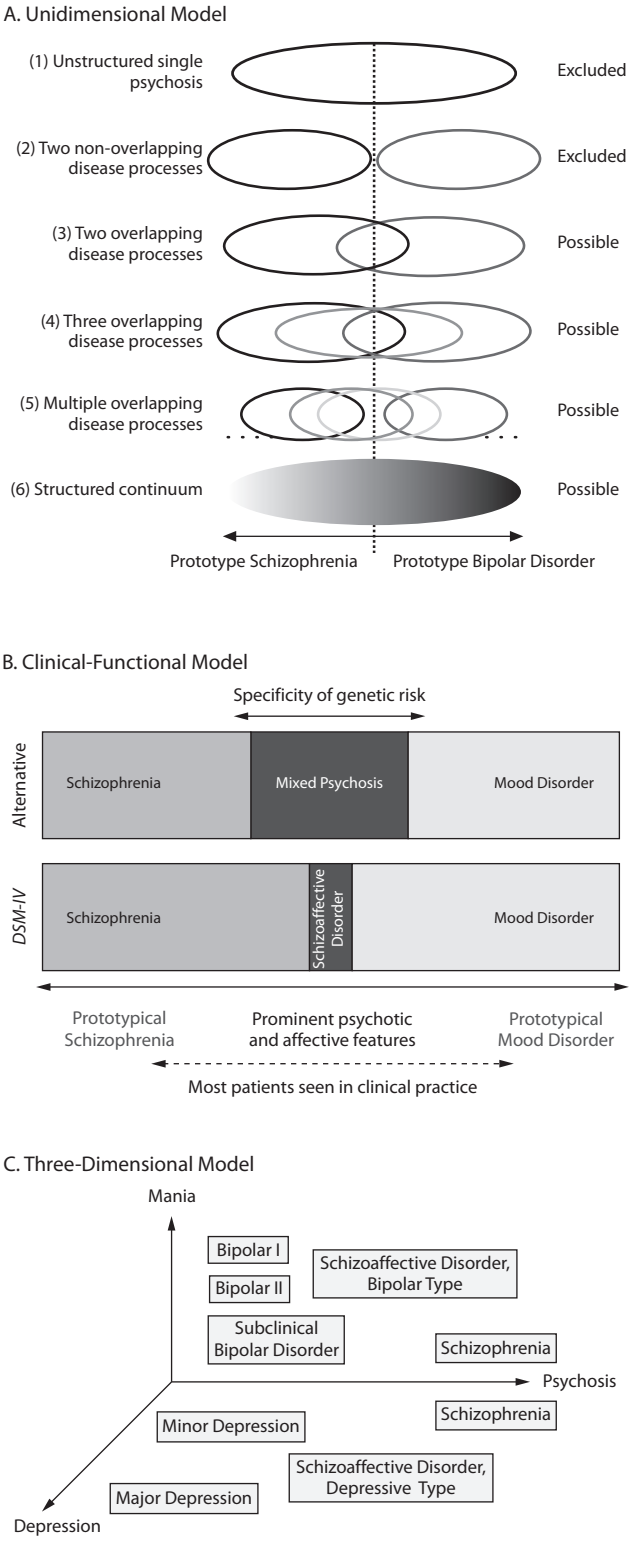
	Pattern in Relation to Schizoaffective Disorder	
Variable	Schizophrenia	Mood Disorder
Proportion of patients never married	↑/ =	↓/ =
Proportion of patients unemployed	↑	↓
Family morbidity		
Schizophrenia risk for relatives of probands	↑/ =	↓/ =
Mood disorder risk for relatives of probands	↓/ =	↑/ =
Dexamethasone suppression test (level of cortisol or proportion of nonsuppressors)	↓	↑
Structural neuroimaging (frequency of anatomical changes)	=	↓/ =
Symptom severity		
Global evaluation	=	=
Psychotic	↑/ =	↓/ =
Negative	↑	↓
Affective	↓/ =	↑/ =
Cognitive deficit	↑/ =	↓/ =
Social premorbid adaptation	↓	↑

[a]Based on Cheniaux et al.[1]
Symbols: for all variables except social premorbid adaptation, ↑ = more than, ↓ = less than, = = the same as; for social premorbid adaptation, ↑ = better than, ↓ = worse than, = = similar to.

Genes that confer risk specifically for schizoaffective disorder were sought by Hamshere and colleagues[8] among probands with schizoaffective disorder, bipolar type who had at least 1 family member with schizophrenia, bipolar I disorder, or schizoaffective disorder, bipolar type. Chromosome 1q42 appeared to influence risk for features of both schizophrenia and bipolar disorder, ie, the combination of both features as seen in schizoaffective disorder. The location of this chromosome is close to the *disrupted in schizophrenia 1* (DISC1) gene that has been associated with risk for schizophrenia, bipolar disorder, and schizoaffective disorder. Chromosomes 22q11 and 19p13 were identified as possibly influencing susceptibility to psychosis in the schizophrenia-bipolar spectrum. An abnormality in the calreticulin gene on chromosome 19 was also found in a family case[9] of schizoaffective disorder.

A large genome-wide association analysis[10] of bipolar disorder suggested that the gene encoding the γ-aminobutyric acid–A ($GABA_A$) receptor β1, β3, β4, and β5 subunits influenced the risk for schizoaffective disorder, bipolar type.

Figure 1. Model of Possible Biologic-Genetic Overlap Between Schizophrenia and Bipolar Disorder[a]



[a]Reprinted with permission from Craddock et al.[2]
Abbreviation: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

A smaller study[11] examined whether variation in the gene encoding brain-derived neurotrophic factor (BDNF) is implicated in schizophrenia and mood disorders. Individuals with schizoaffective disorder and mood disorders had higher frequencies of carrying 2 copies of the most common 5-marker BDNF haplotype than healthy controls or individuals with schizophrenia. Other studies have found additional genes and gene abnormalities that may be associated with schizoaffective disorder and/or schizophrenia or bipolar disorder.[12]

Neuroimaging

Abrams and colleagues' review[12] of neuroimaging studies found that, compared with healthy control subjects, patients with schizoaffective disorder had reductions in cerebral volume in the temporal and frontal regions, including both gray and white matter. The patterns of reduction were similar to those found in patients with schizophrenia and bipolar disorder. Abnormalities were most consistently found in the hippocampus and parahippocampal gyri. A review of brain imaging studies by Bora and colleagues[13] concluded that both similarities and differences existed between patients with schizophrenia and psychotic bipolar disorder. For example, the authors suggested that temporal volume reductions, possibly associated with hallucinations, may be greater in schizophrenia than in schizoaffective disorder.

Additionally, in schizophrenia and schizoaffective disorder, white matter abnormalities appear to worsen over time; pathology in first-episode patients with either disorder was less substantial than that found in patients with chronic illness.[14] However, in bipolar disorder patients, white matter network connectivity abnormalities appeared in the prefrontal and frontal regions, and an overlap in white matter pathology was found between schizophrenia and bipolar disorder.[15,16]

Electrophysiology

In electrophysiologic studies,[13] patients with schizoaffective disorder have been found to have abnormal event-related potentials, localization of sensory-evoked magnetic fields, and eye movements.[12] More similarities seem to exist in these abnormalities among schizoaffective disorder and bipolar disorder with psychotic features than among schizoaffective disorder and schizophrenia.[12] For example, when suppression of the P50 auditory evoked potentials (ie, the ability to ignore irrelevant auditory stimuli) was compared, deficits in patients with schizoaffective disorder were less severe than those in schizophrenia patients.[17] Among patients with schizoaffective disorder, bipolar type, only those who carried a variant allele of the nicotinic receptor gene (CHRNA7) showed a P50 impairment, but patients with schizophrenia had the P50 impairment irrespective of nicotinic receptor status.[18] Furthermore, anomalous asymmetry compared with controls was reported in patients with schizophrenia and schizoaffective disorder when 2 subcomponents of the M100 auditory evoked field were examined.[12,13,19]

Neuroendocrine Functioning

Neuroendocrine functioning in patients with schizoaffective disorder has been examined using clonidine, apomorphine, and methylphenidate challenge.[12] Findings suggest that neuroendocrine disturbances may be related to dysfunction in either the emotional regulation domain or information processing domain, or in both domains. Lesser growth hormone response to clonidine was shown among patients with major depressive disorder and schizoaffective disorder than among schizophrenia subjects and controls.[20] Greater growth hormone response to apomorphine challenge test was found in women with a history of affective disorders who developed postpartum psychosis compared with women with a history of affective disorders who did not develop postpartum psychosis and controls. No influence of life events was shown.[21] Among subjects with schizoaffective disorder or schizophrenia, abnormal growth hormone secretion and decreased response to methylphenidate were seen compared with controls.[22]

Neurochemistry

A few studies have examined the neurochemical determinants of schizoaffective disorder compared with schizophrenia or mood disorders. One review[23] reported that individuals with schizophrenia and schizoaffective disorder shared some patterns of neurochemical abnormalities (eg, cerebrospinal fluid norepinephrine and platelet serotonin levels), but other patterns were more alike among those with schizoaffective disorder and bipolar disorder (eg, platelet serotonin profiles). A subsequent review[12] suggested that neurotransmitter abnormalities correlate less with particular disorders than with symptom severity, especially psychosis, and outcome measures such as length of inpatient treatment.

Neuropsychology

Neuropsychological studies suggest that similar patterns of cognitive impairment, general IQ levels, and motor and language impairment occur in schizophrenia, schizoaffective disorder, psychotic bipolar disorder, and psychotic depression, but that the greatest impairment seems to occur in patients with schizophrenia.[24,25] Evidence suggests that, while some cognitive impairments are shared across the disorders (eg, deficits on backward digit span, which tests working memory), some impairments are associated with particular symptoms (eg, more severe mood symptoms influence perseverative errors).[12]

A review[13] examined cognitive studies of patients who were symptomatic as well as those in which patients had been stabilized. In patients with acute schizoaffective disorder and schizophrenia, few differences were found in neurocognitive performance (eg, context memory). However, when stabilized patients were compared, those with schizoaffective disorder tended to have milder deficits than patients with schizophrenia; for example, patients with schizoaffective disorder performed better on theory of mind and visual motor tasks than those with schizophrenia. This difference between state and trait assessments suggests that acute illness impairs cognition more in patients with schizoaffective disorder. In contrast, cognitive deficits in schizophrenia generally seem to change little after stabilization.[25] However, many studies in the review[13] did not differentiate between schizophrenia subtypes, such as paranoid versus disorganized nonparanoid schizophrenia, which may affect cognitive function differently.[12]

Few studies compared cognition in schizoaffective disorder with that in affective disorders. A meta-analysis[26] examined performance in 12 cognitive domains in individuals with schizophrenia versus those with schizoaffective disorder or affective psychosis. Schizophrenia patients performed worse than the other groups in 6 of 12 domains. However, differences between the groups were small and results were heterogeneous. Between-group differences were influenced by worse negative symptoms, a greater proportion of male probands, and a younger age at onset in the schizophrenia group. The authors concluded that neuropsychological data did not provide sufficient evidence for categorical differences between schizophrenia and schizoaffective disorder or psychotic mood disorders. Likewise, Abrams and colleagues' meta-analysis[12] supported the finding that schizophrenia and schizoaffective disorder share similar deficits in information processing, but that subtypes of schizophrenia might show cognitive differences.

PSYCHOSOCIAL FUNCTIONING

Levels of premorbid adjustment and psychosocial functioning appear to differ between patients with schizoaffective disorder and schizophrenia. When functioning at different periods of life was examined using the Premorbid Adjustment Scale (PAS), patients with schizoaffective disorder showed significantly better premorbid adjustment than patients with schizophrenia as of late adolescence (Table 2).[27] For example, scholastic performance and peer relationships were more impaired in patients with schizophrenia than in those with schizoaffective disorder. More correlations were found between PAS life periods and symptom severity in the schizophrenia group than in the schizoaffective group. However, these differences may be related to an earlier illness onset in patients with schizophrenia.

Another study[28] found that, compared with patients with schizophrenia, patients with schizoaffective disorder had better premorbid adjustment in the academic domain, but patient groups did not differ significantly in the social domain. Having fewer negative symptoms was associated with having better academic and social functioning. Bellack and colleagues[29] compared role functioning and social skills in patients with schizophrenia (with or without negative symptoms), bipolar disorder, and schizoaffective disorder. While patients with schizophrenia without negative symptoms had similar levels of social disability compared with patients with schizoaffective disorder or bipolar disorder, those with negative symptoms were more

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Table 2. Differences in Specific Areas of PAS Life Periods Between Patients With Schizophrenia or Schizoaffective Disorder[a,b]

	Schizophrenia		Schizoaffective Disorder	
Life Period Functioning Area	Mean	SD	Mean	SD
Late adolescence	n = 38		n = 23	
Sociability/withdrawal	2.3	1.9	1.9	1.7
Peer relationships[c]	2.3	1.7	1.2	1.3
Scholastic performance[d]	3.5	1.6	2.1	1.3
Adaptation to school[c]	2.7	1.9	1.5	1.5
Sociosexual aspects	3.2	1.8	2.8	1.8
Adulthood	n = 33		n = 21	
Sociability/withdrawal	4.0	1.5	3.1	2.1
Peer relationships[e]	3.9	1.7	2.8	1.8
Sociosexual aspects[e]	4.3	1.9	3.1	1.8
General	n = 41		n = 24	
Educational[c]	3.2	1.8	2.0	1.4
Employment/school functioning	2.4	1.8	1.7	1.5
Deterioration of work/school performance	2.6	2.0	2.0	1.8
Frequency of job change	2.7	1.8	1.8	1.7
Independence[e]	4.4	1.4	3.5	1.5
Highest level of functioning[e]	4.2	1.3	2.9	1.4
Sociopersonal adjustment[e]	4.2	1.1	2.8	1.4
Interest in life[d]	3.6	1.3	2.2	1.3
Energy level[d]	4.0	1.4	2.6	1.5

[a]Adapted with permission from Saracco-Alvarez et al.[27]
[b]Data for childhood and early adolescence were omitted as no significant differences were found. Lower PAS scores equal better functioning.
[c]$P < .01$.
[d]$P < .001$.
[e]$P < .05$.
Abbreviation: PAS = Premorbid Adjustment Scale.

impaired than patients in the other 2 groups on most measures of social disability, even when duration and severity of illness were comparable.

In Cheniaux and colleagues' review[1] of psychosocial outcomes in patients with schizoaffective disorder, schizophrenia, and mood disorders, the schizophrenia group had the greatest proportion of never-married patients, followed by schizoaffective disorder and then mood disorders (see Table 1), although the results were relatively similar. Rates of unemployment followed the same pattern, but the groups were even more widely separated. Premorbid social adaptation was lowest in patients with schizophrenia, was better in those with schizoaffective disorder, and was highest in those with mood disorders. Cognitive deficits were greatest in patients with schizophrenia, followed by those with schizoaffective disorder and then mood disorders. Cognitive deficits can negatively affect social and vocational functioning; patients may forget meetings and job interviews or fail to reach educational goals. Adverse psychosocial repercussions may result, such as being unemployed, having low self-esteem, and having reduced opportunities to live independently, mix with others, and take an active part in society.

CONCLUSION

Schizoaffective disorder is a diagnostic entity derived from clinical observation of co-occurring psychotic and affective symptoms. Data from neurobiologic and psychosocial outcomes research suggest that phenomenologically, clinically, and neurobiologically, schizoaffective disorder patients occupy an intermediate position between more severely disturbed schizophrenia patients and less severely impaired affective disorder patients. However, data could equally support the hypotheses that schizoaffective disorder is a variant of either schizophrenia or mood disorders, a state of comorbidity of schizophrenia and a mood disorder, or a unique psychiatric disorder. Additional research into biomarkers of the illness and treatment course and response is needed to further elucidate the etiology of schizoaffective disorder and improve outcomes in these patients.

Drug names: apomorphine (Apokyn), clonidine (Catapres, Jenloga, and others), methylphenidate (Ritalin, Methylin, and others).
Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

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