

Schizoaffective Disorder: Evolution and Current Status of the Concept



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SUMMARY

Schizoaffective disorder as a diagnostic entity is of particular present-day relevance; however, the concept of schizoaffective disorder, and its management and prognosis remain contentious. Descriptions of the disorder have varied over time. In this literature review, after tracking the evolution of the concept and nosology of schizoaffective disorder, research findings are summarized. This review takes a broad overview of the epidemiology, neurobiology, clinical presentation, diagnostic validity and stability, treatment, course, and outcome of schizoaffective disorder. Importance is given to the distinctness of schizoaffective disorder, and the overlap with schizophrenia and mood disorders, and problems associated with the construct are examined. Possible ways to treat the construct in the future in the best interest of patients, clinicians, and researchers are discussed.

Keywords: Schizoaffective disorder, concept, evolution, nosology, schizophrenia

Abbreviations

SAD: Schizoaffective disorder; **SCZ:** schizophrenia; **MD:** mood disorder; **BPD:** bipolar disorder; **MDD:** major depressive disorder.

INTRODUCTION

The diagnostic entity schizoaffective disorder (SAD) is of particular present-day relevance; however, descriptions of the disorder have varied over time. Its concept, management, and prognosis have been long-debated and its status remains contentious. The present literature review aimed to bring attention to this exciting concept. The relevant literature was searched via the electronic databases PsycINFO, EMBASE, MEDLINE, PubMed, Google Scholar, and Online Contents using the search terms SAD, bipolar disorder, schizophrenia, nosology, classification, diagnosis, concept, evolution, and controversy. Article titles and abstracts were reviewed for relevance, and if deemed applicable the full-text articles were retrieved. Only English-language articles were included in this

review, and all included articles were published between 1978 and 2013

Evolution of the Concept

Emil Kraepelin divided the endogenous psychoses into dementia praecox, which is characterised by progressive deterioration and a poor outcome, and manic-depressive insanity, which is characterised by a remitting course and favorable outcome (Kempf et al. 2005; Marneros 2003). Zendig highlighted weaknesses in Kraepelin's dichotomy concept, noting that not all cases can be classified into the 2 categories, and Kurt Schneider coined the term, cases-in-between, to refer to such cases (Marneros 2003). Jacob Kasanin used the term schizoaffective psychosis to describe patients with both schizophrenic and affective symptoms (Tsuang and Simpson

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1984). In the ensuing months and years schizoaffective psychosis became a popular term used to describe the co-occurrence of severe affective and psychotic syndromes that didn't fit into Kraepelin's categories. The concept of a diagnostic entity apart from schizophrenia and manic depression, but with features of both began to expand (Maier 2006).

Evolution of Nosological Systems

In the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I, 1952), SAD was considered a subtype of SCZ (schizoaffective type of schizophrenia). The long-term course, however, was said to be basically schizophrenic in nature. DSM-II, 1968 continued to regard SAD as a sub-type of SCZ, but divided SAD into excited and depressed subtypes (Fochtmann et al. 2009; Procci 1989). The Research Diagnostic Criteria (Spitzer et al. 1978) was the first to operationalize and define specific criteria for SAD. SAD was defined as the acute co-occurrence of a full mood syndrome and one of a set of core schizophrenic symptoms, such as bizarre delusions, first-rank symptoms, and hallucinations. In DSM-III 1980 SAD was still given a residual category—a diagnosis of last resort. It was defined as a psychotic illness with a mixture of schizophrenia and affective symptoms that cannot satisfy the diagnostic criteria for schizophrenia, major affective disorders, and schizophreniform disorder (Procci 1989; Tsuang and Simpson 1984). In the DSM-III-R 1987 though SAD was more clearly defined, it was still grouped under psychotic disorders not elsewhere classified (Fochtmann et al. 2009; Kempf et al. 2005). The DSM-IV, 1994 gave more importance to the diagnosis of SAD, placing it under the category of schizophrenia and other psychotic disorders (Fochtmann et al. 2009; Kempf et al. 2005).

In the eighth revision of the International Classification of Diseases (ICD-8 1965) SAD was a part of schizophrenic psychosis without a separate category. ICD-9 (1975) also considered SAD a subtype of schizophrenic disorders, but with characteristics akin to MD. ICD-10 (1994), however, placed SAD in the category schizophrenia, schizotypal, and delusional disorders (Bannerjee et al. 1991; Procci 1989).

Comparison of ICD and DSM

A number of differences exist between the 2 major nosological systems. ICD-10 conceptualizes SAD as episodic and defines the episode. DSM-IV-TR, without mentioning the long-term course as episodic or continuous, states that there must be an “uninterrupted” period of illnesses, where mood and schizophrenic symptoms occur concurrently, that is, not sequentially, with an interruption in between. ICD-10 requires typically schizophrenic symptoms (criterion A-D) for diagnosing SAD. In DSM-IV-TR symptoms meeting criterion A, i.e. any delusion, hallucination, or even negative symptoms,

are sufficient. In addition, DSM-IV-TR requires delusions and hallucinations to occur for at least 2 weeks during the same episode, in the absence of prominent mood symptoms (APA 1994; WHO 1992). Both ICD-10 and DSM-IV-TR are criticized for, that, there is no justification mentioned for chronological specification regarding the co-existence of schizophrenic and affective symptomatology. Mood and schizophrenic symptoms occurring concurrently are included in DSM-IV-TR, but if they occur sequentially—that is, one after the other—why are they excluded? Additionally, both diagnostic systems are criticized for focusing on a short temporal period without consideration of the long-term course and longitudinal aspect of the illness (Marneros 2003).

What is SAD?

Ever since Kasanin's description of the schizoaffective psychoses researchers have sought to answer the following questions: *Is SAD the co-occurrence of SCZ and an MD? Is SAD a variant of SCZ with prominent mood symptoms? Is SAD a severe MD in which episode-related psychotic symptoms fail to remit completely between episodes? Is SAD the mid-point of a continuum between SCZ and MD, or is it a separate condition?*

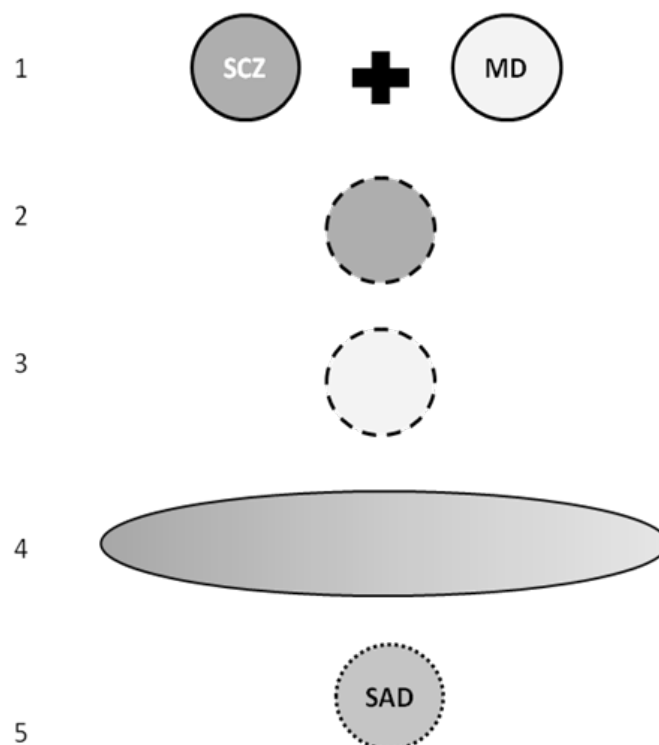


Figure 1. What is SAD?

Robins and Guze (1970) described 5 phases to achieve diagnostic validity for any disorder: clinical description, laboratory studies to objectify characteristics of the disorder, delimitation from other disorders, follow-up studies to look for stability over a period of time, and family studies to determine

prevalence among relatives. In the following sections of this review we will summarize researchers' attempts over the years to understand SAD and disentangle it from SCZ and MD.

Current Research: Findings and Controversies

Epidemiology

The literature includes little data concerning the epidemiology of SAD and variation in its definition makes precise estimates of prevalence based on the available data difficult. The estimated prevalence of SAD ranges from 0.2%-1.1% (Scully 2004; Marneros 2003; Erlenmeyer-Kimling et al. 1997; Kendler et al. 1993, 1985). Even at its most frequent, SAD is reported to be as prevalent as SCZ and less common than BPD. Regarding age of onset, although there is heterogeneity of findings, most studies report that the range of age of onset is similar to that of BPD and SCZ, and that median age of onset is between that of SCZ and BPD (Abrams et al. 2008). Though there is a degree of variability in many epidemiological variables of SAD, there is agreement across studies that SAD occurs more often in females; it is thought that about 66% of persons with SAD are female (Lenz et al. 1991; Marneros et al. 1990; Angst et al. 1980).

Clinical Features

Some studies report subtle differences in psychopathology, which may be useful in diagnosing SAD, SCZ, and BPD, whereas others have refuted such claims, suggesting that in clinical practice subtle distinctions in clinical symptoms do not help categorize diagnoses. Most studies characterize SAD as having a high level of pre-morbid function, as compared to SCZ, an identifiable precipitating event, periodic and rapid onset of symptoms, and a relatively high rate of remission (Tsuang et al. 2009).

Heredity

Family studies report that SAD occurs at a higher rate among relatives of probands with SCZ and MD. SCZ and MD occur at higher rates among relatives of probands with SAD, as compared to the general population (Bertelsen and Gottesman 1995; Kendler et al. 1993; Gershon et al. 1982). Research findings indicate that MD, SAD, and SCZ occur along a continuum—from mood disorders to mood disorders accompanied by psychosis to schizophrenia. A twin study that included monozygotic and dizygotic twin pairs, and in which probands met Research and Diagnostic Criteria (RDC) (Spitzer et al. 1978) for SCZ, SAD, or manic syndrome reported that there were significant genetic correlations between all 3 syndromes (Cardno et al. 2002). Hamshere et al. (2009) conducted a genome-wide genetic association study to explore the genetic utility of 7 different diagnostic categories related to MD and SAD. Compared to other diagnostic

subsets, SAD, bipolar type, as defined by Research Diagnostic Criteria (Spitzer et al. 1978), had a significant excess of independent association signals.

Broadly defined, bipolar SAD (RDC) was inferred to be the most biologically valid diagnostic subset. Linkage studies have shown many overlapping chromosomal regions shared by SCZ, SAD, and MD. Molecular genetic studies have shown susceptibility genes common to SCZ, SAD, and MD, i.e. *DISC1*, *NRG1*, *DAOA*, and genes related to development of glutamate-signaling pathways (Craddock et al. 2006; Fallin et al. 2005; Green et al. 2005; Hodgkinson et al. 2004). Variations in the *BDNF* gene, in addition, were reported to play an important role in affective dysregulation across diagnostic categories (Lencz et al. 2009). The above findings indicate there is an overlap in genetic susceptibility across traditional diagnostic entities, which may have important implications, as these studies show that there is an overlap in the biological basis of disorders that have been classified as distinct entities since 1960's. In addition, the studies also point out that genetic susceptibility exists for SAD as a construct.

Neuropsychology

Research has shown that like SCZ, SAD is also associated with impairment in various frontally mediated cognitive functions (Abrams et al. 2008). Beatty et al. (1993) reported that patients with SAD had less severe impairment of temporal lobe-dependent functions, such as delayed recall, than patients with SCZ. Stip et al. (2005) observed that SAD patients had less severe deficits in posteriorly mediated cognitive functions than SCZ patients. In a recent study that aimed to objectify the distinction between SCZ and SAD based on various tasks involving frontal, temporal, and occipital lobar function, The SCZ patients exhibited more severe impairment in all cognitive measures studied, relative to the SAD patients and controls (Heinrichs et al. 2008).

Neuro-imaging

Comparisons of SAD with SCZ and BPD have shown there is significant overlap. A reduction in cerebral volume—including both gray and white matter—particularly in the temporal and frontal regions has been observed in patients with SAD, and the most consistent finding across studies was abnormalities in the hippocampus and para-hippocampal gyri (Abrams et al. 2008; Getz et al. 2002).

Electrophysiology

EEG findings in SAD patients have been compared to those in SCZ and BPD patients. Martin et al. (2007) reported that of 18 SAD patients, 12 had BPD-like and 6 had SCZ-like EEG findings. Mathalon et al. (2010) conducted a study that directly compared SAD and SCZ. Normal P300 amplitudes

were observed in the SAD patients, which were significantly higher than those in the SCZ patients and indistinguishable from those in the controls. P300 latency and reaction time were both equivalently delayed in SCZ and SAD patients, as compared to healthy controls.

Diagnostic Stability

Shrivastava and Rao (1999) followed up 76 first-episode SAD patients for more than 2 years, during which time the diagnosis remained consistent in only 18.4% of patients. Schwartz et al. (2000) conducted a 2-year follow-up study that included 547 patients diagnosed with psychosis. The diagnosis remained stable in 92% of those with SCZ, 83% of those with BPD, and 74% of those with MDD, but in only 36% of SAD patients. Salvatore et al. (2009) followed up 500 patients with first-episode psychosis for 2 years. The number of cases diagnosed as SAD increased from 0.2% to 12.2% during the course of the study. These findings show that a nearing two-third of patients with an initial diagnosis of SCZ or MD have the same diagnosis during follow-up, whereas the stability of a diagnosis of SAD is poor.

Diagnostic Reliability

Jager et al. (2011) studied inter-clinician reliability of a diagnosis of SAD using different nosological definitions. The Kappa-value varied between a maximum of 0.63 when ICD-10 research criteria were used to 0.08 when DSM-III-R criteria were used. Figures ranged between poor and moderate inter-clinician agreement. Vollmer-Larsen et al. (2006) re-evaluated the clinical diagnosis of SAD by clinicians using a computerized operational criteria checklist. Only 10% of patients with a clinician-made diagnosis of SAD met the ICD-10 criteria for SAD and none met the DSM-IV criteria. In addition, use of ICD-10 and DSM-IV criteria for diagnosing SAD resulted in selection of different samples of patients. The question remains, is the diagnosis of SAD used incorrectly or are the diagnostic criteria deficient?

Treatment

Systematic research on the pharmacological treatment of SAD is lacking. The few published studies have a limited ability to be compared because of differences in the diagnostic criteria used and because of using combination diagnostic groups. As such, there is no consensus on treatment recommendations. For acute treatment antipsychotics are used often, as acutely ill patients often have prominent psychotic symptoms. For maintenance the treatment of choice is usually guided by SAD subtype. Mood stabilizers are usually used for the bipolar subtype, anti-depressants for the depressive subtype, and antipsychotics for persistent psychosis. Clozapine is used when the above treatment strategies fail. In cases of incomplete

response to drugs, electroconvulsive therapy (ECT) is useful (Malhi et al. 2008). Paliperidone recently became the first specific drug to be approved by the US FDA for the acute treatment of SAD; however, other first- and second-generation antipsychotics may be equally effective in patients with SAD. Atypical antipsychotics with neuroleptic and mood-stabilizing properties may be ideal for monotherapy, but studies in this regard are lacking (Kantrowitz and Citrome 2011).

Course and Outcome

The course of SAD is variable, with recovery rates ranging between 29% and 83% across study samples. About 20%-30% of patients exhibit a deteriorating course with persistent psychotic symptoms. In about 10% of patients the relative prominence of affective and schizophrenic symptoms shifts over time. In general, the prognosis of SAD lies between that of SCZ and MD (Jager et al. 2011; Abrams et al. 2008; Malhi et al. 2008).

What then, is SAD?

To date, research findings on SAD show that there are significant differences between international nosological systems and epidemiological rates are variable. There are neurobiological commonalities between SAD, SCZ, and MD, but there are no clear boundaries between the clinical presentations of these entities. Diagnosis of SAD is less reliable and stable than that of SCZ and MD. There are no specific treatment approaches for SAD; clinicians use an individualized combination of techniques used to treat SCZ and MD. The outcome of SAD is generally more favorable than that of SCZ, but worse than that of MD. Studying the overlap between SAD, SCZ, and MD Cheniaux et al. (2008) reported that it is less likely that SAD represents an atypical form of SCZ or MD; SCZ, MD co-morbidity; or an independent mental disorder, however, it remains unclear if SAD constitutes a heterogeneous group composed by both SCZ and MD patients, or if it is a mid-point along a continuum between SCZ and MD.

Is the current concept of SAD valid?

According to the criteria for establishing diagnostic validity proposed by Robins and Guze (1970), the entity SAD does not appear to have passed the test. researchers argue that SAD does not deserve to exist as a diagnostic entity (Maier 2006), but other researchers have lobbied for the retention of its status, though some alterations in its definition may be necessary. Marneros (2007) suggested that though there was no evidence that SAD is a unique neurobiologically defined nosological entity, such evidence for other psychotic, depressive, or bipolar disorders is similarly lacking. Patients with SAD differ in social adaption, symptomatology, and prognosis than those with SCZ; Marneros (2007) thinks that the clinical

diagnosis of SAD is useful for physicians, provides hope for patients, and should not be abandoned in favor of changing theoretical ideas. Researchers in favor of retaining SAD as a diagnostic entity have argued that the findings of studies on SAD do not indicate the non-existence of SAD, but rather that the present diagnostic criteria are deficient.

How to Transcend the Controversy

Conceivable options for the future include removal of SAD from diagnostic classifications, a return to Kraepelin's dichotomous classification with broad concepts of SCZ and MD, use of a continuous spectrum model with a dimensional diagnostic approach, subdivision of classical categories into multiple diagnostic entities, and a combination of approaches.

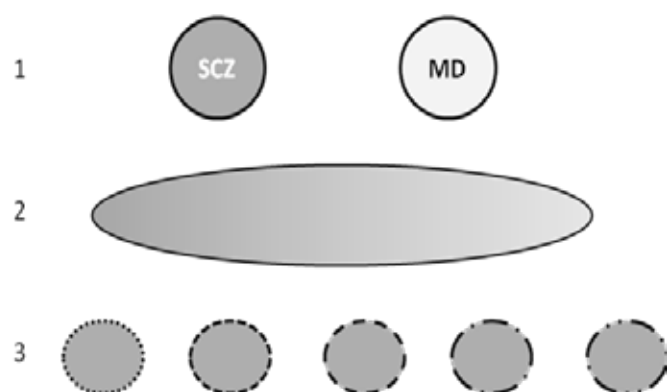


Figure 2. How to transcend the controversy.

There is preference among clinicians and patients for using the term SAD over SCZ due to difference in disease course and overall better outcome with SAD. There is also interest among pharmacological researchers and manufacturers for developing better drugs for patients with prominent psychotic and mood symptoms. As such, dismantling the SAD diagnosis is unlikely to happen in the near future. In addition, considering the knowledge gained from all the research conducted in the post-Kraepelinian dichotomy era, a dichotomous classification does not seem compatible today. Perhaps the best solution to the controversy would be the use of a continuous spectrum model with a dimensional diagnostic approach, subdivision of classical categories into multiple diagnostic entities, or a combination of these approaches.

1. Continuous Spectrum Model with Dimensional Diagnostic Approach

Recent psychopathological and neurobiological research shows that functional psychoses exist as a continuous spectrum compatible with a dimensional concept for diagnosis. In a dimensional approach psychiatric disorders are classified based on dimensions of neurobehavioral dysfunction, but a pure dimensional approach may not agree with current

scientific and clinical practice (which primarily use a categorical approach). Treatment guidelines, in addition, are based upon categorical diagnoses. Moreover, dimensions of psychopathological syndromes have low stability and long-term utility (Heckers 2012). These issues make switching drastically to a purely dimensional diagnostic approach impractical.

2. Multiple Diagnostic Entities

ICD and DSM have used multiple diagnostic categories to classify psychiatric disorders. Some researchers propose expansion of the existing systems via sub-categorizing functional psychoses based on course and outcome. They recommend abstaining from the neurobiological validation of diagnostic entities, suggesting that this method of classification could improve individual treatment of psychiatric disorders. Those that oppose this method have argued that diagnostic splitting based on favorable versus unfavorable outcome would encourage discrimination and increase stigma (Jager et al. 2011).

3. Combination of Dimensional and Categorical Approaches

A recent consensus is that a combination of approaches could be the answer to the SAD debate. A dimensional approach could be used to address the cross-sectional clinical picture, whereas a categorical approach could be used to specify the diagnosis, course, and outcome.

The newly released DSM-V (APA 2013) used such a combination approach as is the proposal in ICD-11 (Jager et al. 2011). In the DSM-V SAD has been placed under the group 'Schizophrenia Spectrum and Other Psychotic Disorders'. The primary change in the SAD category is the requirement that a major mood episode be present for a majority of the disorder's total duration after criterion A has been met. SAD is hence viewed as a longitudinal instead of a cross-sectional diagnosis. In addition to the above modifications, as with schizophrenia the severity and core symptoms of SAD are to be assessed on a dimensional scale (APA 2013).

Conclusions and Future Directions

Since the time Jacob Kasanin first introduced the term schizoaffective, there has been tremendous interest in research on this borderline group of disorders. Researchers have agreed that there are a group of patients resembling SCZ and MD, but simultaneously not distinct from SCZ or MD. Research findings have shown the heterogeneity among patients in this group in all respects, including incidence-prevalence, clinical presentation, and treatment response. The diagnosis and treatment of SAD remain contentious.

Despite great interest and much research during the previous century, SAD remains an enigmatic and much-debated entity. Its validity as a diagnosis remains questionable, and at the same time, the value of the diagnosis—to patients, clinicians, and researchers—cannot be over estimated. Many of the questions concerning SAD (like other “established” psychiatric disorders) have been unanswered. Also, the heterogeneity of clinical presentation, and neurobiological research findings of psychiatric disorders that are on a continuous spectrum, among others, call into question, the status given to other disorders such as schizophrenia. As such, there is an emerging consensus that SAD need not be dismantled as a diagnostic entity; instead, we must accept that with currently available technology and knowledge we may not apply all neurobiological and other research findings to every-day clinical use. Though the categorical-dimensional debate continues, researchers currently support a combination that makes use of the advantages of both the approaches. It is of utmost importance that there be congruity between the ICD and DSM classification systems, which would preclude further confusion of an already ambiguous subject, help clinicians improve their treatment of SAD patients, and improve the work of all researchers studying SAD.

Further research on all aspects of SAD is needed, with an independent focus on SAD populations rather than considering them as a part of studies on SCZ or MD. Studies that employ modern technology might also need to bridge the gap that presently exists between neurobiological findings and clinical practice.

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