Review

Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders

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Abstract

Background: Since its first definition in the literature, schizoaffective disorder (SAD) has raised a considerable controversy regarding its clinical distinction from schizophrenia (SCH) and mood disorders (MD) as well as its validity as an independent nosological category.
Objective: Investigate the validity of SAD as a discrete nosological category and its relationship with SCH and MD.
Method: A systematic literature review of clinical trial that compared SAD with SCH and/or MD patients was carried out throughout MEDLINE, psycINFO, Cochrane Library, SCIELO and LILACS databases.
Results: Evaluation of demographic characteristics, symptomatology, other clinical data, dexamethasone suppression test, neuroimage exams, response to treatment, evolution and family morbidity indicated that SAD occupies an intermediate position between SCH and MD. Literature review also failed to indicate a clear cut distinction between SAD and SCH or MD.
Discussion: Present analysis indicated that SAD cannot be interpreted as atypical forms of SCH or MD. SAD also does not appear to represent a SCH and MD comorbidity or yet an independent mental disorder. It is argued that SAD might constitute a heterogeneous group composed by both SCH and MD patients or a middle point of a continuum between SCH and MD.

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Contents

1. Introduction ...................................................... 210
2. Method ......................................................... 211
3. Results ......................................................... 211
   3.1. Demographic data ............................................... 212
   3.2. Family morbidity ............................................... 212

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1. Introduction

Since its first description in the literature (Kasanin, 1933), schizoaffective disorder (SAD) has raised a considerable amount of discussion about its definition. As suggested in its denomination, SAD represents an association between schizophrenic and affective symptoms. However, there are divergences regarding which symptoms should be considered and the type of temporal relationship between these two groups of symptoms to define this mental disorder (McElroy et al., 1999). For example, in RDC (Spitzer et al., 1978) and ICD-10 (World Health Organization, 1993) SAD is characterized by simultaneous and equally prominent affective and psychotic symptoms, particularly Schneider's first-rank ones. DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) also specify the concurrent presence of affective and psychotic symptoms. However, differently from RDC and ICD-10, DSM-III-R and DSM-IV require, during the same episode, an additional period of at least two weeks in which delusions or hallucinations are present, in the absence of prominent affective symptoms.

In parallel to the issue of SAD definition, there is much debate about its existence (Maier, 2006). The construct validity of mental disorders has been controversial throughout the history of psychiatry and remains an important problem nowadays (Widiger, 1997). This issue is particularly more problematic regarding SAD due to the uncertainty about its relationship to schizophrenia (SCH) and mood disorders (MD).

The SAD controversy and its relationship with SCH and MD can be formally stated in six different possibilities. Accordingly, SAD could be interpreted as an atypical form of SCH, with affective symptoms (Evans et al., 1999), what is related to the idea that Schneider’s or Bleuler’s symptoms are pathognomonic for SCH. Conversely, for some authors (Akiskal, 1996; Lake and Hurwitz, 2006) SAD might be an atypical form of MD, with schizophrenic symptoms.

A third possibility views SAD as a form of SCH and MD comorbidity, in which the same patient would suffer simultaneously from both SCH and MD. Based on epidemiological data which indicate the high rates of SCH and MD prevalence, Kendler et al. (1995) concluded that the co-occurrence of both of these disorders is highly probable, which in turn would be equivalent to SAD.

A fourth possibility considers SAD as an independent illness, distinct from both SCH and MD (Tsuang, 1991). This “third psychosis” possibility has its roots in classical authors, such as Kasanin (1933), who observed clinical cases which could not be classified neither as SCH nor manic-depressive illness. However, this view of SAD as a “third psychosis” does not receive much support from the literature. For example, several studies indicated that SAD diagnosis has a low stability in comparison to SCH and MD (Forrester et al., 2001). The low stability of SAD diagnosis probably occurs because, in a longitudinal evaluation, a polymorphic course is observed in the majority of SAD patients (Maj and Perris, 1990; Marneros et al., 1988). Indeed, some patients that receive a cross-sectional SAD diagnosis, based on the RDC, ICD-10 or DSM-IV, presented in their past clinical history multiple syndromes, such as pure affective, pure schizophreniform, or schizoaffective episodes of different polarity. Therefore, it is difficult to envision SAD as specific disorder since its clinical presentation sometimes can be identical to those observed in SCH or MD.

Against the “third psychosis” possibility there is also the fact that same diagnosis among the relatives of SAD probands is fairly rare. Among the first-degree relatives of SAD patients MD diagnoses predominate and there is an excessive number of cases of SCH (Kendler et al., 1995). Besides, there are several reports of pairs of monozygotic twins in which one member has SAD while the other suffers from SCH or MD (Bertelsen and Gottesman, 1995).

A fifty possibility proposes that SAD represents a heterogeneous group, composed by both SCH and MD.
patients (Levitt and Tsuang, 1988). A parallel between this possibility and the RDC subdivision of SAD in mainly schizophrenic subtype and mainly affective subtype can be traced. Accordingly, the mainly schizophrenic SAD patients would suffer from SCH, whereas the mainly affective SAD ones would suffer from MD (Tsuang and Coryell, 1993).

All these five possibilities discussed above taken for granted that SCH and MD are independent mental disorders. However, it has been suggested that there is only a single psychosis and that SCH and MD might constitute extremes of a continuum. Consequently, the sixty and last possibility proposes that SAD occupies an intermediary position on this continuum (Crow, 1990).

Several results are in agreement with this view. For example, there are important similarities between SCH and bipolar disorder regarding demographic aspects, such as lifetime prevalence, gender distribution and age of onset (Maier et al., 2006). According to some authors (Andreasen and Akiskal, 1983; Taylor and Amir, 1994), clinical presentation alone does not permit a reliable differentiation between SCH and MD. Moreover, several family (Lapierre, 1994), twin (Bertelsen and Gottesman, 1995) and other genetic studies (Berrettini, 2003; Craddock et al., 2006) suggest a close relationship between SCH and MD. Finally, some studies that investigated the structural alterations in brain using computed tomography (Rieder et al., 1983), the season of birth (Torrey et al., 1996) and the history of obstetric complications (Gunduz et al., 1999) failed to find a distinction between SCH and MD.

The main argument against to the possibility of a continuum between these two disorders came from family studies. Assuming that SAD constitutes an intermediate form of SCH and MD then it would be expected a high prevalence of SAD among offspring from couples in which one individual had SCH and the other had a MD. However, this is not what is observed. SAD is a rare condition among these offspring, in opposition to the high prevalence of SCH and MD (Bertelsen and Gottesman, 1995).

Based on this controversy, the purpose of the present work was to perform a systematic survey of the literature in order to investigate each of these six possible outcomes, and consequently examine the construct validity of SAD as an independent nosological category.

2. Method

Clinical studies describing comparisons of at least ten SAD patients with at least ten SCH and/or MD subjects were identified in five databases: MEDLINE, psy-INFO, Cochrane Library, SCIELO and LILACS, up to November 12, 2006. Searches were performed using schizoaffective and schizo-affective key-words. Only the references with abstracts and original articles were considered. Review articles, case reports, letters to the editor and books’ chapters were not included. There was no search for unpublished works. Citations within a paper were also included as an additional source of references. Two of the authors (EC and JLF) screened all the abstracts and made a decision about its importance for the present work.

3. Results

The initial search retrieved 2743 citations from MEDLINE, 3556 from psyCINFO, 676 from Cochrane Library, 5 from SCIELO, and 475 from LILACS, with many overlaps among the databases. A total of 217 abstracts were classified as potentially relevant according to our criteria. We could not get access to 13 articles. After the appraisal of the full-text articles, 155 citations were selected and 49 were excluded.

The most common reason for exclusion of articles was the absence of distinction between SAD from SCH or MD patients in the analysis of results in studies about SCH or MD. Other common reason for article exclusion was the lack of comparison between SAD with SCH and/or MD patients. Many articles with a small sample size or whose sample sizes were not informed were also excluded.

Among the selected articles there were many in which the samples of SAD patients were represented by just one subtype of the disorder — schizomanic or schizoaffective, bipolar or unipolar, mainly schizophrenic or mainly affective. It was also common to find articles in which several subtypes of SAD were mixed in a same sample, without having a distinction among them. The same pattern was also found across the samples of MD patients: bipolar or unipolar, with or without psychosis, with congruent or incongruent mood psychotic symptoms. Besides, in the comparison between SAD and MD, not always patients of the same polarity — schizobipolar and bipolar, by example — were analyzed; and, in many studies, schizoaffective patients — which, by definition, are psychotic — were contrasted with individuals with a non-psychotic MD.

When the subtype of SAD or MD, as discriminated in the article, was considered relevant for the result, then this issue was pointed in the text. However, for the sake of simplicity, just SAD, SCH and MD categories, without any subdivision, were employed. The symbols “>” and “<” were used to assign the relationship
between SAD with SCH and/or MD. No attempt was made to compare SCH and MD patients.

Considering all the investigated aspects, the differences about the results among the studies apparently are not related to the criteria employed for the diagnoses of SAD, SCH and MD. Table 1 summarizes the general pattern results of the variables investigated.\(^1\) These variables were grouped in six main categories: demographic data, family morbidity, complementary exams, symptomatology, other clinical variables, clinical evolution and response to drug treatment.

### 3.1. Demographic data

Twenty-three studies failed to show any difference between SAD and SCH regarding gender distribution, whereas twelve reports found more females among SAD patients as compared to SCH. When the comparison was done between SAD and MD, thirty-two of the studies revealed no difference between these two groups, whereas four found fewer women in SAD when compared to MD. Only two studies found proportionally more women in SAD than in MD (Inui et al., 1998; Williams and McGlashan, 1987). However, in the sample of Inui et al. (1998), there were only twelve SAD patients, all females. Williams and McGlashan (1987), in their turn, included just bipolar MD patients in the comparison with SAD patients, whose subtypings were not considered.

With regards to marital status, the proportion of SAD patients that never married was equal (five studies) or inferior (six studies) to SCH patients. On the other hand, the proportion of SAD patients that never married was equal (nine studies) or superior (three studies) to MD patients. Rate of employment across these three nosological categories seems to follow the same pattern. SAD patients presented a level of unemployment similar (two studies) or lower (three studies) than SCH patients. Finally, unemployment rates among SAD patients were similar (four studies) or higher (one study) in comparison to MD patients.

### 3.2. Family morbidity

Twenty-six studies investigated the rates of the risk to SCH or MD for the relatives of SCH, SAD and MD probands. These studies indicated that SCH risk for the relatives of SAD probands is equal (ten studies) or

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\(^1\) Due to space limitation, we refer the reader interested in more detailed information about Table 1 to the following address: http://www.landeira.org/echeniaux.
probands; however, considering the risk to depression, there was no difference between both.

The polarity between SAD and MD patients and the presence or not of psychotic symptoms among MD patients influenced significantly the results. When the samples were composed by schizomanic (or schizobi-polar) and manic (or bipolar) probands, there was a clear tendency for both groups presenting similar family histories and distinguishing themselves from SCH probands (Benabarre et al., 2001; Nardi et al., 2005; Pope et al., 1980). However, the same did not repeat between schizodepressive and depressive probands (Coryell and Zimmerman, 1988; Maj et al., 1991). Still in relation to this aspect, SAD probands became closer to MD ones when these were psychotic than were not (Maj et al., 1991).

Three studies (Baron et al., 1982; Gershon et al., 1988; Kendler et al., 1986) indicated that SAD mainly schizophrenic type patients and SCH patients have a very similar family history. Otherwise, it was not clear if the same occurs between SAD mainly affective type patients and MD patients (Baron et al., 1982; Gershon et al., 1982; Kendler et al., 1986).

3.3. Complementary exams

Several authors investigated the dexamethasone suppression test (DST) in patients with SAD and their comparison to SCH and MD. Two studies found higher levels of cortisol or a larger proportion of non-suppressors among SAD when compared to SCH patients. Three studies did not find any difference between SAD and MD patients in the DST. However, Maj (1986) and Meador-Woodruff et al. (1988) found lower levels of cortisol in SAD patients when compared to MD, but no difference between the two groups in relation to the number of patients with a positive result in the test. A divergent result was obtained by Sauer et al. (1984). They verified higher levels of cortisol and proportion of non-suppressors in schizodepressive patients in comparison to non-psychotic depressive ones, although schizomanic and non-psychotic depressive patients had presented similar responses.

Five studies investigated structural neuroimaging changes in SCH, SAD and MD patients. Three of them employed computed tomographic scans (Gewirtz et al., 1994; Jones et al., 1994; Rieder et al., 1983), whereas two used magnetic resonance imaging (Getz et al., 2002; Lewine et al., 1995). Four of these studies did not find a clear distinction between SCH and SAD in relation to brain structural changes. Three studies also were not able to find any differences in neural brain structure between SAD and MD. Jones et al. (1994) found an enlargement of lateral ventricles in patients with SCH and SAD, but not in the patients with MD, and enlargement of third ventricle in the three groups. Finally, Getz et al. (2002) observed that bipolar patients presented a bigger size of pallidum than the observed in SAD patients. Nevertheless, there was no difference between the patients of two groups in relation to the size of striate and caudate nucleus.

3.4. Symptomatology

Eight studies employed different global evaluation scales to compare SAD patients with SCH or MD. None of them found any significant statistical differences among the three groups. The intensity or frequency of psychotic symptoms in SAD patients was equal (ten studies) or lower (ten studies) than in SCH patients. As expected, SAD patients had equal (six studies) or more intense or frequent psychotic symptoms (six studies) when compared to MD patients. Negative symptoms followed the same the pattern. SAD patients presented similar (eight studies) or less intense negative symptoms (eight studies) in relation to SCH patients, but equal (seven studies) or higher (five studies) negative symptoms when compared to MD patients. The opposite pattern was observed in relation to affective symptoms. SAD patients presented similar (seven studies) or more intense affective symptoms (four studies) in relation to SCH patients, but equal (six studies) or less intense (five studies) affective symptoms when compared to MD patients.

Regarding neuropsychological evaluations, SAD patients presented similar (fourteen studies) or lower (five studies) cognitive deficit than SCH patients, and similar (seven studies) or higher (five studies) cognitive deficit than MD patients. There are not many studies which investigated insight deficit, or unawareness of the mental disorder, among SAD patients (four studies). Patients with SAD presented equal (two and three studies, respectively) or less (two and one studies, respectively) insight deficit than SCH and MD patients.

3.5. Other clinical variables

Six studies investigated the premorbid social adaptation of SAD patients in comparison to SCH and MD. These studies indicated that SAD patients were equal (one study) or better (five studies) than SCH ones. One study indicated that SAD was equal whereas five studies pointed out that they were worse when compared with MD patients.
Nineteen studies indicated that SAD begins at the same age of SCH, whereas only two studies pointed out that SAD had a later onset as compared to SCH. When compared to MD, seventeen studies indicated an absence of difference, whereas six studies revealed that SAD begins in younger individuals than MD.

Eggers (1989) found that SAD patients had presented a bigger number of previous episodes of illness than SCH patients. Angst et al. (1980) observed a higher frequency of episodes in MD patients than in SAD ones. However, five studies failed to find differences between SAD and MD concerning this variable.

A preponderance of SAD about the amount of previous hospitalizations since these patients presented equal or higher amount of this variable to either SCH (nine and four studies, respectively) or MD (nine and five studies, respectively) patients, was observed.

Regarding suicidal behavior, no differences was found among these three mental disorders (seven studies), with the exception of two studies which found more suicidal attempts among SAD in comparison to SCH and/or MD patients.

According to this review, the rates of comorbidity with substance related disorders in SAD were higher than in SCH (Nardi et al., 2005), lower than in MD (Advokat et al., 2005), or similar to these two disorders (five studies).

3.6. Clinical evolution

Forty-seven studies investigated the clinical evolution among SCH, SAD and MD patients. Results are clear cut and indicated that SAD had the same (fifteen studies) or a more favorable (twenty-four studies) clinical evolution when compared to SCH patients, and equal (twenty-three studies) or less favorable (twenty-one studies) evolution when compared to MD patients.

3.7. Response to drug treatment

Eleven studies investigated SCH, SAD and MD responses to psychotropic drug treatment. Some clinical trials compared SAD with SCH or MD (only bipolar) patients in relation to the use of mood stabilizer drugs (Bouman et al., 1986; Hayes, 1989) or an atypical antipsychotic (Ciapparelli et al., 2004; Keck et al., 1995; Zarate et al., 2000). Summarizing the results, SAD patients presented identical (three studies) or better (three studies) responses to drug therapy when compared to SCH patients and equal (nine studies) or an inferior (three studies) response when compared to MD patients. As an exception, Zarate et al. (2000) found that SAD patients presented a better response to quetiapine than unipolar depressive patients; however, there was not a difference between those patients and bipolar affective ones.

4. Discussion

The present paper attempted to review empirical studies published in the literature in order to examine the validity of SAD as a nosological category and its relationship with SCH and MD. As it can be observed in Table 1, SAD seems to occupy an intermediary position between SCH and MD, but it is not clearly distinct from the two classical major psychoses (SCH < SAD < MD or SCH > SAD > MD). This general pattern was already expected, since SAD is defined as a mixture of SCH and MD characteristics.

There were only a few exceptions to this pattern. As presented in this table, SAD patients presented less insight deficit, higher number of hospitalization and higher frequency of suicidal behavior when compared to SCH and MD. The lower level of insight deficit among SAD patients in comparison to MD is based a single study (Pini et al., 2004) and needs further confirmation. SAD is related to a higher number of hospitalizations than SCH probably because it constitutes a more episodic disorder (Eggers, 1989). The higher number of hospitalizations among SAD patients in comparison to MD might be associated to the degree of symptom severity. Schizoaffective episodes, by definition, are always psychotic, and usually are more severe than affective episodes, which in turn, might not be psychotic. Finally, the largest risk to suicide among SAD patients might be due to the simultaneous presence of psychotic and mood symptoms in this disorder. Both of these symptom groups are related to suicidal behavior in SCH and MD, respectively.

Our results do not support the possibility which suggest that SAD might represent an atypical form of SCH, since many studies found differences between SCH and SAD (SCH < SAD or SCH > SAD) whereas others evidenced an identity between SAD and MD (SAD = MD). The same can be said about the possibility of SAD being an atypical form of MD. Many studies found differences between SAD and MD (SAD < MD or SAD > MD) whereas others verified an equivalence between SCH and SAD (SCH = SAD).

Our analysis also weaken the possibility of SAD constitutes a comorbidity between SCH and MD. If this were correct, SAD would tend to be always equidistant to SCH and MD (SCH = SAD = MD, SCH < SAD < MD or SCH > SAD > MD). Although these patterns have
been frequent, various studies found similarities between SCH and MD (SCH=SAD<MD or SCH=SAD>MD), or vice versa (SCH=SAD<MD or SCH>SAD=MD).

Table 1 also demonstrated that SAD could not be unequivocally distinguished from SCH or MD. Although some results have indicated differences between SAD and SCH or MD (SCH>SAD>MD or SCH<SAD<MD), many studies found similarities between SAD and SCH or MD (SCH=SAD; SAD=MD; SCH=SAD=MD). These last results argue against the possibility that SAD constitutes a discrete mental disorder.

Our analysis did not allow ruling out the view that SAD represents a heterogeneous group of mental disorders. According to this proposition, individuals who meet the criteria for SAD diagnosis might represent, in fact, a mixed group of both SCH and MD patients. Therefore, the common discrepancies among the results of the diverse studies might be explained according to the sample of SAD patients (Tsuang and Coryell, 1993). In studies with a preponderance of SAD mainly affective patients, SAD would be similar to SCH (SCH=SAD<MD or SCH=SAD>MD). Conversely, in studies with a preponderance of SAD mainly affective patients, SAD would be similar to MD (SCH=SAD<MD or SCH>SAD=MD). Finally, when the sample are composed by similar amounts of SCH and MD patients, SAD would appear equidistant to SCH and MD (SCH=SAD=MD, SCH<SAD<MD or SCH>SAD>MD).

Family morbidity studies which employed the RDC subdivision of SAD support the view that SAD represents a heterogeneous group of SCH and MD patients. Baron et al. (1982), Gershon et al. (1988) and Kendler et al. (1986) found that family histories of mainly schizophrenic SAD probands and SCH probands were similar. In the same vein, Baron et al. (1982) and Kendler et al. (1986) found the same relationship between mainly affective SAD and MD probands. It must be noted that Gershon et al. (1982) did not observe this last finding.

Grossman et al. (1984) and Coryell and Zimmerman (1986) investigated the clinical evolution of SAD patients classified according to this RDC subdivision. Although Grossman et al. (1984) did not find any differences between the two SAD subtypes, Coryell and Zimmerman (1986) detected a more favorable clinical evolution among mainly affective SAD as compared to mainly schizophrenic SAD patients. Since MD patients usually have better evolution than SCH patients, this result is in agreement with the heterogeneous group view of SAD.

The present study also did not permit excluding the possibility that SAD represents an intermediate position on a continuum between SCH and MD. This possibility adopts a dimensional model of psychiatric diagnosis and considers the existence of a single psychosis. Accordingly, different results are found in the comparisons between SAD and SCH of MD depending on if SAD patients’ characteristics are closer to the SCH extreme (SCH=SAD<MD or SCH=SAD>MD), to the MD extreme (SCH<SAD=MD or SCH>SAD=MD) or to a point between them (SCH=SAD=MD, SCH<SAD<MD or SCH>SAD>MD). This explanation is basically the same proposed in relation to heterogeneous group possibility, which, differently, is linked to the categorical model of diagnosis.

Coherently with this model of continuum, two family studies indicated that the risk to unipolar depression among the relatives of SCH patients was significantly higher than among the relatives of normal controls (Gershon et al., 1988; Maier et al., 1993). Besides, several studies seem to indicate that the occurrence of psychotic symptoms, especially if incongruent with mood, makes MD closer to SCH. In a family study, Maj et al. (1991) verified that the unipolar type SAD probands were clearly distinguished from the non-psychotic depressed ones, but not from the psychotic depressed ones. In the same study, no difference was observed between SCH and depressed probands with incongruent psychotic symptoms. Toni et al. (2001) found that manic patients with mood-incongruent psychotic symptoms presented significantly more cases of SCH in family that those with mood-congruent ones. Harrow et al. (2000) showed that the MD patients with psychotic symptoms presented a more favorable evolution than SCH patients, but a less favorable evolution than non-psychotic depressed ones. Furthermore, the MD patients with incongruent psychotic symptoms presented a worse evolution when compared with patients with congruent psychotic symptoms. All these results are in accordance to the hypothesis of a spectrum between psychotic, bipolar and unipolar disorders (Akiskal, 2006). However, in contradiction to that, Tsuang and Coryell (1993) compared, in relation to evolution, two groups of depressed patients, one with congruent psychotic symptoms and another with incongruent ones, and found no differences between them.

Marneros et al. (1988) established a clear distinction between schizoaffective episode and schizoaffective disorder. The former was defined cross-sectionally while the latter was defined longitudinally. This distinction is still absent in the current classification manuals. In DSM-IV, just like schizophreniform disorder, SAD essentially represents a provisional diagnosis, employed when a SCH or MD typical course is not yet
clearly defined. This occurs because SAD diagnosis criteria seem to be more appropriate to a psychiatric episode than to a discrete nosological category. An episode versus disorder distinction is already present in the MD chapter of DSM-IV, where there are criteria for the diagnoses of major depressive and manic episodes, which do not constitute nosological categories, and criteria for the diagnosis of bipolar disorder and major depressive disorder, among others. Accordingly, it would be interesting if mental disorder classification systems could incorporate diagnosis criteria for both schizoaffective episode and schizoaffective disorder. This would certainly allow a better investigation of SAD and increment its eventual validity.

As a whole, our study indicated that SAD does not comprise 1) an atypical form of SCH; 2) a variant of MD; 3) a comorbidity between SCH and MD; and 4) an independent disorder. Unfortunately, our systematic literature review did not allow choosing between two other possibilities, which view SAD as a heterogeneous group of patients or a middle point of a continuum between SCH and MD. However, these two last possibilities are part of a more general issue, which is related to the dimensional versus categorical diagnostic dilemma in current mental disorder classification systems.

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