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Schizophrenia dissection by five anxiety and depressive subtype comorbidities: Clinical implications and evolutionary perspective

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ABSTRACT

Twenty patients with DSM5 schizophrenia were comprehensively and formally assessed by an experienced psychiatrist. All subjects were assessed for: positive and negative psychotic symptoms; social anxiety; panic anxiety; obsessive compulsive disorder, atypical depression; major depression; suicide risk; and global assessment of functioning. Different profiles of clinical presentation and symptom evolution emerged for patients with schizophrenia who had co-morbid depression (15%), OCD (15%), panic or limited symptom attacks (55%) and social anxiety (5%). At least eighty percent of the sample had one or more of these co-morbidities. Summing up, the data support our previous finding that panic is highly prevalent in Schizophrenia with Auditory Hallucinations (> 73% here, versus 100% before), and panic was paroxysmally concurrent with voice onset. Moreover, characteristic clinical findings may help point clinicians to five specific co-morbidity psychosis subtypes. Moreover, co-morbidity dissection of psychotic diagnoses recalls and parallels the historical psychopharmacologic dissection of non-psychotic anxiety and depressive subtypes diagnoses. Larger studies should further test and explore these preliminary findings.

1. Introduction

Co-morbidities in schizophrenia have been increasingly described, explored and treated since recent years have seen increasing awareness of the presence and potential significance in schizophrenia co-morbidities. This is consistent with epidemiological research showing the high prevalence of psychiatric co-morbidities found in schizophrenia patients (Bermanzohn et al., 2001). The main changes from DSM-IV to 5 are related to the organization of psychiatric disorders, particularly with regard to a broader clustering among groups of diagnostic categories. In the case of schizophrenia. the proximity of psychotic disorders and premorbid personality traits is presented in the section on "Schizophrenia Spectrum and other Psychotic Disorders" by the sequential description of schizotypal (personality) disorder, delusional disorder and schizophrenia (Regier et al., 2013).

Other research supports the idea that Major Depression (MDD; encompassing Melancholia and Atypical Depression), Obsessive-Compulsive Disorder (OCD), Panic Disorder (PD), Social Anxiety (SA) may be the five core diagnoses in non-psychotic patients; as well as the most common schizophrenia co-morbidities. They are also the five core emotionally painful syndromes in an evolutionary theory that posits their Darwinian evolution from five corresponding primeval altruistic instincts (Kahn, 2013; Braga et al., 2013). The transition from non-psychotic anxiety or depressive disorder to a psychotic form is more likely to occur in patients with frontal cortex hypo-frontality or increased dopaminergic activity - consistent with considerable research in those areas (Kahn, 2013).

Co-morbid disorders with schizophrenia can predict increased overall symptom severity and worsened prognosis (Karpov et al., 2016). On the other hand, adequate diagnosis and treatment of these conditions can produce significant amelioration of co-morbidities, as well as both positive and negative psychotic symptoms (Bermanzohn et al., 2001; Kahn et al., 1987). Historically, co-morbid syndromes have long been employed for diagnostic subtyping of psychosis, include such now widely accepted diagnoses as psychotic Bipolar Disorder and Delusional Depression (ICD-10).

In the same way, psychosis in the setting of the anxiety disorders may reflect distinct pathophysiologic forms of psychosis. The possible

role of anxiety is suggested by research in DSM diagnosed schizophrenia patients, showing that there is a general reduction of brain GABA activity which statistically correlates with positive symptom severity (Frankle et al., 2015; Glausier and Lewis, 2017). A large scale Australian study reported that the 12-month prevalence of anxiety disorders in schizophrenia was 56%, and that panic was associated with an increased family history of schizophrenia. More importantly, treatment of the co-morbidity appears to improve person-specific outcomes (Bosanac et al., 2016). Occasionally, co-morbidities are first recognized after the use of an atypical antipsychotic. The relation is especially well documented in the literature for OCD (Grillault-Laroche and Gaillard, 2016). While it is possible that atypical antipsychotics may trigger OCD onset, it is also possible that undiagnosed OCD preceded psychosis onset, and then became more apparent with decreased psychosis and improved cognition. Poyurovsky et al. (2012) recently proposed diagnostic criteria for a Schizo-Obsessive disorder based on finding different clinical, epidemiologic and brain functional patterns in previous studies (Poyurovsky, 2013).

Kahn et al. (1987) reported that cases with schizophrenia and panic attacks had substantial improvement in panic symptoms when they were treated with adjunctive alprazolam, and also improvement in their positive and negative symptoms. They later observed the simultaneous paroxysmal onset of panic with auditory hallucinations, as if voices were psychotic panic attacks in a "Panic Psychosis" (Kahn and Meyers, 2000). Subsequent research supported this idea that auditory hallucinations and panic symptoms were paroxysmal and concurrent, based on the structured Panic and Schizophrenia Interview (PaSI), and also in response to a 35% CO_2/65% O_2 challenge test. The CO_2 challenge is a commonly accepted trigger of panic attacks in susceptible persons (but not in control subjects) – and which can also sometimes trigger auditory hallucinations (Savitz et al., 2011).

The present investigators have also observed a longitudinal relationship between clinically diagnosed social anxiety disorder and later diagnosis of paranoid delusional disorder in four cases (Veras et al., 2015). Considerable research points to significant and similar psychotic features in non-psychotic social anxiety (Lysaker et al., 2010a), and many papers have explored generally the theoretical interconnections between anxiety and psychosis (Pallanti et al., 2013). Since adjunctive SSRI treatment may improve delusional disorder outcome, exploration of delusional disorder as psychotic social anxiety should be examined (Veras et al., 2015).

This pilot study assessed features of five core depressive and anxiety co-morbidities in schizophrenia using well-validated scales. As a secondary goal, subgroups of cases with specific co-morbidities were examined for such possible sub-syndromal distinctions as particular positive and negative symptoms, time course, and other clinical variables.

2. Methods

2.1. Participants

Twenty consecutive patients diagnosed with DSM5 criteria schizophrenia were evaluated for this pilot study. Assessment was conducted at a psychiatric hospital in Campo Grande, Mato Grosso do Sul State, Brazil. Patients were treated by usual hospital psychiatrists, with no standard treatment protocol.

2.2. Procedure

The study was approved by the Local Ethics Committee. Subjects were first informed about the research by their clinical team. Interested cases were recruited into the study after their schizophrenia diagnosis was confirmed by record review. All subjects signed an informed consent, with additional written authorization obtained from subjects' relatives.

After an experienced researcher (ABV) used DSM5 criteria to

reconfirm schizophrenia diagnosis, a retrospective symptom assessment started with a broad clinical interview about patients` history and symptomatic evolution. History was not obtained from family, but uncertain information was further clarified using additional data from the files, staff members and familiars. Cognitive impairment may have diminished retrospective recall.

This clinical assessment was followed by the structured interviews, scales and inventories. A socio-demographic and clinical questionnaire was used to collect information on age, sex, ethnic group, family income, age at first symptoms (psychosis, depression and anxiety), age at first admission, medication use and known clinical co-morbidities. Group ethnicity in Brazil was determined by researchers' assessment of ethnic ancestry, including patients' self-classification. Caucasian means European Descent, Afro means African Descent, and Aboriginal denotes Native Brazilian in the same sense as USA Native American, Canadian First Nation, or Aboriginal Australian. Depressive or anxiety symptom onset was also determined when those specific disorders were each assessed.

The Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-CV) was used to assess the current diagnosis of schizophrenia, subtypes, and current or past psychiatric co-morbidities. Current symptoms of schizophrenia were detailed by: Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Current co-morbidities were examined with: Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987), Yale Brown Obsessive Compulsive Disorder Scale (YBOCS) (Goodman et al., 1989), Panic and Schizophrenia Interview (PaSI) (Savitz et al., 2011), Atypical Depression Diagnostic Scale (ADDS) (Stewart et al., 1993), Calgary Depression in Schizophrenia Scale (CDSS) (Addington et al., 1993), Columbia Suicide Severity Scale (C-SSRS) (Posner et al., 2011) and Global Assessment of Functioning (DSM-IV GAF). Interviews were conducted over three sessions of 60–90 min, 2–4 days apart, by ABV or a trained master's degree psychology student (TG).

2.3. Statistical analysis

Average and standard deviation (SD) were used to evaluate descriptive data. The Spearman correlation coefficient was used to observe the relationship between the symptom intensity and the other variables in the sample. $P < .05$ was considered statistically significant in this pilot study.

3. Results

The subjects were mostly female (65%), often in their fourth decade, of African descent (70%), mostly not high school graduates (80%), and with limited income (detailed in Table 1). These socio-demographic characteristics are consistent with the patient population afflicted with severe mental disorders under public health service care in Brazil.

Clinically, all patients had schizophrenia: 70% (14 of 20) had the paranoid subtype. Sixty percent (12 of 20) had at least one psychiatric co-morbidity, according to strict DSM-5 criteria. The most commonly present co-morbidities were MDD (n = 3), OCD (n = 3) and alcohol or other illicit drugs addiction (n = 3). Although only one patient each had DSM co-morbid social anxiety and panic disorder on the SCID, there were seven patients (35%) who had concurrent full DSM panic attacks with auditory hallucinations (Table 2), three more with limited symptoms (panic with three other symptoms), and another with full panic attacks in agoraphobic situations. Altogether, 55% patients (11 of 20) presented panic anxiety. Excepting the agoraphobic patient, all patients with panic anxiety (10 of 11) did report experiencing them while having auditory hallucinations. Limited symptom panics may be nearly as clinically significant as full panics (Pané-Farré et al., 2013), and panic concurrent with hallucinations would be overlooked by the