

# Prevalence and correlates of anxiety disorders in psychotic illness

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## **Abstract- Prevalence and correlates of anxiety disorders in psychotic illness**

**Background:** Comorbid anxiety disorders in psychotic illness are reported in the international literature as highly prevalent and have a significant negative impact on patient outcomes. Local literature describing such comorbidity in the South African population is limited and clinically, anxiety symptoms are seldom recognised or treated in patients with psychotic disorders. More data on prevalence rates across psychotic disorder diagnoses, as well as sociodemographic correlates would aid recognition, diagnosis, and treatment, and potentially improve clinical outcomes in this population.

**Method:** We performed a secondary analysis of an existing database which comprised data from participants of three previous studies. The sample was made up of patients from Valkenberg Hospital and healthcare facilities in its catchment area. All patients had a diagnosis of a psychotic disorder. Socio-demographic information was collected using a structured questionnaire. Clinical information and diagnosis was determined using the Structured Clinical Interview for DSM (SCID-I). Rates of comorbid anxiety disorders were compared across various sociodemographic categories.

**Results:** The overall prevalence of any anxiety disorder in the entire sample (N=226) was 14.6% (n=33), 95% CI [10.27-19.89%]. The most common anxiety disorder comorbidities were, in descending order, panic disorder (n=12, 5.31%; 95% CI [2.77-9.09%]), PTSD (n=9, 3.98%; 95% CI [1.84-7.42%]), specific phobia (n=7, 3.10%; 95% CI [1.25-6.28%]), anxiety disorder not otherwise specified (n=7, 3.10%; 95% CI [1.25-6.28%]), social phobia (n=4, 1.77%; 95% CI [0.48%-4.47%]), generalised anxiety disorder (n=4, 1.77%; 95% CI [0.48-4.47%]), substance-induced anxiety disorder (n=4, 1.77%; 95% CI [0.48-4.47%]) and obsessive compulsive disorder (n=2, 0.88%; 95% CI [0.11-3.16%]). There was a significant association between diagnosis and the presence of post-traumatic stress disorder (PTSD), with the schizoaffective disorder group having a higher rate of PTSD (13.3% vs. 3.3% in schizophrenia, 3.2% in substance-induced mood/psychotic disorder and 0% in bipolar I disorder) (Fisher's exact test, p=0.039). In turn, there was a trend level association between diagnosis and the presence of panic disorder (PD), with schizoaffective disorder patients having higher rates of PD (16.6% vs. 4.1% in schizophrenia spectrum, 3.2% in substance-induced mood/psychotic disorder and 2.2% in bipolar I disorder) (Fisher's exact test, p=0.052).

A significant association was found between level of education and the presence of PTSD, with higher rates of PTSD in patients with seven or less years of education (8.8%) compared to lower rates in those with 8-12 years of education (5.3%) and > 12 years of education (0%) (Fisher's exact test,  $p=0.020$ ).

**Conclusion:** The overall prevalence of anxiety disorders in psychotic illness was lower than what has been described in previous literature. Prevalence rates of individual anxiety disorders were also lower than previously published literature. Possible reasons for this include use of the SCID which utilises a strict diagnostic hierarchy, that the majority of the sample were in-patients, no use of self-report questionnaires or other anxiety-specific diagnostic instruments, or possible geographical and/or ethnic differences in South African patients. The most frequent comorbid anxiety disorders in our study were panic disorder and PTSD. This is out of keeping with other literature which has mostly found obsessive compulsive disorder and social anxiety disorder to be the most common anxiety comorbidities in psychotic illness. Further research into comorbid anxiety in psychotic disorders is needed, particularly amongst South African populations.

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## Abbreviations

<b>AD</b>	Anxiety disorder
<b>ARMS</b>	At-risk mental state
<b>BDNF</b>	Brain-derived neurotrophic factor
<b>BPD</b>	Bipolar disorder
<b>DSM</b>	Diagnostic and statistical manual of mental disorders
<b>DSM-5</b>	Diagnostic and statistical manual of mental disorders, 5th Edition
<b>DSM-IV</b>	Diagnostic and statistical manual of mental disorders, 4th Edition
<b>GAD</b>	Generalised anxiety disorder
<b>HAM-A</b>	Hamilton anxiety scale
<b>MA</b>	Meta-analysis
<b>OCD</b>	Obsessive compulsive disorder
<b>OCS</b>	Obsessive compulsive symptoms
<b>PD</b>	Panic disorder
<b>PTSD</b>	Post-traumatic stress disorder
<b>SAD</b>	Social anxiety disorder
<b>SASH study</b>	South African Stress and Health study
<b>SCID</b>	Structured Clinical Interview for DSM-IV-TR
<b>SCZ</b>	Schizophrenia
<b>SERT</b>	Serotonin transporter
<b>SIMPD</b>	Substance-induced mood/psychotic disorder
<b>SSRI</b>	Selective serotonin reuptake inhibitor
<b>SZA</b>	Schizoaffective disorder
<b>Y-BOCS</b>	Yale-Brown obsessive compulsive scale
<b>5HT1A</b>	Serotonin-1A

# Chapter I: Introduction and Literature review

## 1. Literature search strategy

A literature search was performed on the Medline database through the PubMed portal using combinations of the following terms:

"schizophrenia", "schizophreniform disorder" or "schizophreniform", "psychotic disorder" or "psychosis", "schizoaffective disorder" or "schizoaffective", "bipolar disorder" or "bipolar", "substance-induced psychosis" or "substance-induced psychotic disorder" or drug-induced psychosis" or "drug-induced psychotic disorder", "anxiety" or "anxiety disorder", "generalised anxiety disorder" or "GAD", "post-traumatic stress disorder" or "PTSD", "obsessive-compulsive disorder" or "OCD", "panic disorder" or "panic", "phobia" or "phobic disorders", "social anxiety disorder" or "social phobia".

The search was confined to literature in English and only systematic reviews and meta-analyses from the last 20 years were included. A total of 895 papers were identified, the titles of which were scanned to identify relevant studies, which totalled 37. Additional studies were identified using the reference lists of the papers generated from the original search.

## 2. Summary of the Literature

### 2.1. Introduction

Symptoms of anxiety in psychotic illness have long been recognised and were even described by Bleuler.<sup>1</sup> Although there has been a recent increase in literature looking at this topic, data is still limited and the studies that have been done vary widely in both methodology and outcomes, making analysis of results difficult.<sup>2-4</sup>

It remains unknown whether anxiety in psychotic illness should be viewed as secondary symptoms that occur due to the distressing nature of psychosis, as a comorbidity that occurs as a result of chance or shared risk factors, or whether anxiety features represent part of a prodromal picture or different symptom dimension of the core condition.<sup>5</sup> As a further complicating factor, some

neuroleptic drugs used in psychotic disorders have been associated with treatment-emergent anxiety symptoms.<sup>6-9</sup>

Diagnosis of a comorbid anxiety disorder in people with psychotic illness may be complicated by the hierarchical structure found in diagnostic systems such as the Diagnostic and statistical manual of mental disorders (DSM).<sup>10,11</sup> The way in which the DSM has been structured, is to prioritise certain groups of disorders over others. For example, in diagnostic criteria for anxiety disorders, the DSM requires that the symptoms are “not better accounted for by another mental disorder”.<sup>10</sup> This makes diagnosis of an anxiety disorder difficult and often subjective as, even if all the other criteria for the disorder are fulfilled, it is necessary to decide whether the anxiety symptoms may be accounted for by the primary psychotic diagnosis or not. This has probably led to low rates of diagnosis and recognition of anxiety disorders in schizophrenia in the past.<sup>12</sup> Diagnostic hierarchies have also complicated research as some studies suspend diagnostic hierarchies in their methodologies and others do not.

Clinically, perhaps due not only to diagnostic hierarchies but also because of the dramatic nature of psychotic symptoms, anxiety seems to be seldom recognised, diagnosed or treated in psychotic patients as the psychotic symptoms demand the bulk of clinical attention.

In the literature that is available on anxiety in psychotic illness, prevalence rates are heterogeneous but generally high, often higher than in the general population.<sup>2-4,9</sup> This is of concern as, not only are anxiety disorders themselves disabling and potentially life threatening, but comorbid anxiety in psychotic illness seems to have significant negative effects on outcomes. These effects include decreased levels of social functioning, poorer quality of life, increased suicide risk, higher risk of relapse and poorer treatment response in psychotic illnesses.<sup>13</sup>

With better understanding of anxiety in psychotic illness, increased recognition and treatment could potentially improve outcomes in affected individuals. Moreover, as patterns of comorbidity are recognised, these may give clues into underlying neurobiology of both anxiety and psychotic disorders.

## 2.2. Anxiety and psychosis

Most data have looked at anxiety in specific psychotic disorders. However two major studies measured prevalence of anxiety disorders across several psychotic disorder diagnoses.<sup>13,14</sup> Both found high rates of anxiety disorders across the different psychotic disorders. Cosoff et al<sup>14</sup> found similar prevalence rates (43-45%) of anxiety disorders in schizophrenia (SCZ), schizoaffective disorder (SZA) and bipolar disorder (BPD). In a study by Young et al<sup>13</sup>, significant differences of comorbid anxiety were found between the psychotic disorders, with the highest rate of anxiety disorders in schizoaffective disorder (30.1%), followed by BPD (22.4%) and then schizophrenia (16.7%). The authors hypothesised that higher prevalence in SZA may be associated with more mood features. When assessing rates of each anxiety disorder (AD), panic disorder was found to co-occur most commonly with a psychotic disorder.<sup>13</sup> Some gender differences (Female > male), a low rate of clinical recognition and a higher rate of AD in those with a family history of anxiety disorders were noted.<sup>13,14</sup>

Across the literature of anxiety in psychotic illness, broad variations in results exist. Several possible reasons for this have been suggested. These include: heterogeneity in definitions and sampling methods, small sample sizes and different ratings instruments or diagnostic methods used.<sup>2,5</sup> In addition, the diagnostic hierarchy and whether this has been suspended or not, is another likely source of heterogeneity in the data.<sup>2,9</sup>

There is currently very little understanding of the relationship between psychotic disorders and anxiety. Several hypotheses have been presented including: anxiety as the primary disorder, as a comorbid disorder or caused by treatment for psychosis.<sup>15</sup>

One potential outcome of improved understanding of the relationship between psychosis and anxiety is discovery of common pathophysiological processes. Dysregulation of dopamine, serotonin and glutamate systems are known to be involved in both psychotic and anxiety disorders.<sup>16</sup> Preliminary findings regarding comorbidity of anxiety and schizophrenia, implicate both serotonin transporter (SERT) and brain-derived neurotrophic factor (BDNF) genes as well as the serotonin-1A (5HT1A) receptor.<sup>9</sup> In addition, there is some early data from patients with

schizophrenia and anxiety disorders that describe under-active fear circuitry in response to anxiety-provoking stimuli coupled with heightened autonomic response to neutral stimuli.<sup>9</sup>

### 2.3. Schizophrenia spectrum and anxiety

International data show a high prevalence of anxiety disorders in schizophrenia, with good evidence to indicate that these rates may be higher than the general population.<sup>2</sup> Though significant heterogeneity of the data exists, prevalence of anxiety symptoms in schizophrenia are thought to occur in up to 65% and prevalence of anxiety disorders, diagnosable in up to 38%.<sup>2,9</sup> Social anxiety disorder (SAD) appears to be the most common comorbid anxiety disorder in schizophrenia, followed by post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), generalised anxiety disorder (GAD), panic disorder (PD), simple phobia and agoraphobia.<sup>9</sup>

Diagnosis of anxiety in the context of schizophrenia may prove difficult for a number of reasons. Firstly, positive and negative symptoms of psychosis may make it difficult to identify signs and symptoms of anxiety.<sup>17</sup> Positive psychotic symptoms such as delusions, disorganisation and hallucinations may overshadow the presentation of anxiety. Negative symptoms including decreased emotional expression may prevent clear communication and lead to under-reporting or detection of such symptoms. Finally, both agitation related to psychosis and akathisia (an effect of treatment) may mimic anxiety and make differentiation between the diagnoses more challenging.<sup>9,17</sup>

In order to improve diagnostic accuracy, recommendations include assessment after the acute phase of psychosis has settled, routine use of screening questions for anxiety symptoms and employment of self-report instruments.<sup>9</sup> Specialised rating scales may also aid detection and severity assessment of anxiety disorders in schizophrenia.<sup>16</sup>

In a recent meta-analysis, the prevalence rates of comorbid anxiety disorders were found to be higher in women with schizophrenia, in out-patient settings and when Structured Clinical Interview for DSM-IV-TR<sup>18</sup> (SCID) or additional instruments were used to diagnose anxiety disorders.<sup>2</sup>

Comorbid anxiety disorders appear to have overall negative effects on the functioning, response to treatment and quality of life of patients with SCZ.<sup>2,15</sup> Comorbid anxiety has been linked with

increased severity of psychopathology<sup>5</sup>, increased suicidality, more cognitive impairment, more social withdrawal, poorer functioning, increased likelihood of treatment changes and increased use of services.<sup>9,15,19</sup>

Data regarding treatment of anxiety in schizophrenia is very limited. There is some evidence for the usefulness of risperidone and aripiprazole in obsessive-compulsive symptoms (OCS) and social anxiety. For GAD, some efficacy of quetiapine and olanzapine has been shown. In addition, there is also data to support the use of trifluoperazine, a first generation antipsychotic, for treating anxiety symptoms in schizophrenia. Other treatment options that have been investigated but for which there is little data so far, include the augmentation of antipsychotic medication with selective serotonin reuptake inhibitors (SSRI's), buspirone and pregabalin.<sup>9</sup>

### **2.3.1. Schizophrenia Prodrome**

Anxiety may form part of the prodrome of schizophrenia. In a review of prodromal symptoms of psychosis, Yung and McGorry found that anxiety and obsessive compulsive symptoms are common in this period.<sup>20</sup> One large study of patients assessed as having an at-risk mental state (ARMS) showed that 69% of patients had a diagnosis of a mood or anxiety disorder at the time of initial assessment.<sup>21</sup> A meta-analysis (MA) of the literature on ARMS patients found that, in addition to attenuated psychotic symptoms, 15% of ARMS patients had a comorbid anxiety disorder at baseline assessment.<sup>22</sup> In addition, this MA found that comorbid diagnoses of anxiety or depressive symptoms in ARMS were associated with higher levels of disorganised behaviour, more suicidality and self-harm as well as impaired global functioning, worse apathy and avolition.<sup>22</sup> However, no effect of baseline anxiety or depressive diagnosis on the rate of transition to frank psychotic illness was identified.<sup>22</sup>

In terms of phenomenology, it is unclear whether these anxiety symptoms represent features of a comorbid illness or early symptoms of the psychotic disorder. Moreover, current data does not yet allow accurate predictions about how anxiety symptoms affect the likelihood of an individual developing psychosis.<sup>12</sup>

### **2.3.2. Schizophrenia and panic**

Both panic attacks and panic disorder appear to co-occur commonly with schizophrenia.<sup>2,5</sup> The pooled prevalence rate of panic disorder in a recent meta-analysis was 9.8%.<sup>2</sup>

As with other anxiety disorders, the relationship between panic disorder and schizophrenia remains unclear.<sup>16</sup> Some authors have argued that it may represent a specific subtype of schizophrenia with its own pattern of clinical symptoms, deficits and response to treatment.<sup>12</sup>

There is limited data on treatment of panic symptoms in schizophrenia. Some early data suggests efficacy of alprazolam and clonazepam.<sup>12</sup>

### **2.3.3. Schizophrenia and social phobia**

Social anxiety disorder or social phobia appears to be one of the most prevalent anxiety disorders in people with schizophrenia. Reported prevalence rates vary between 3.6 and 39.5% but in their meta-analysis, Achim et al found a pooled prevalence rate of 14.9%.<sup>2</sup>

Symptoms of schizophrenia and social anxiety disorder may appear superficially similar which can complicate diagnosis.<sup>12,16</sup> The Liebowitz social anxiety scale has been used as an aid in diagnosis and has been found to be a reliable assessment tool in patients with schizophrenia.<sup>23</sup> Both disorders may present with poor social functioning, avoidance, social withdrawal and excessive concerns about negative judgements by others.<sup>12,16</sup>

### **2.3.4. Schizophrenia and obsessive compulsive disorder**

OCD is the most studied comorbid anxiety disorder in schizophrenia.<sup>5</sup> Prevalence of OCS in schizophrenia is estimated at 30.3%<sup>8</sup> and of OCD 12.1%.<sup>2</sup>

The comorbid diagnosis of OCD has been associated with greater disability<sup>15</sup>, younger age at onset of illness, increased rates of hospitalisation, decreased likelihood of being married or employed<sup>24</sup>, greater risk of suicidal ideation and attempts<sup>25</sup>, more positive and negative psychotic symptoms<sup>6</sup>, greater paranoia and first rank symptoms, increased rates of depression and comorbid personality disorder,<sup>26</sup> poorer quality of life and greater social and occupational impairments.<sup>27,28</sup> In addition,

some studies have found more severe neuropsychiatric impairments in patients with OCD and schizophrenia, particularly in certain domains of executive function.<sup>5,29</sup>

Some data suggest that when OCS are treated successfully, symptoms of psychosis also improve.<sup>30</sup> Which treatment is the most efficacious and appropriate in this population remains uncertain.

Paradoxically, although second generation antipsychotic drugs can be effective in treatment of refractory OCD, they appear to have potential to worsen OCS in patients with schizophrenia, and sometimes even cause de novo OCS.<sup>5</sup> Nonetheless, some data shows that clozapine and olanzapine may improve psychotic and obsessive-compulsive symptoms in certain patients with both.<sup>31</sup>

In terms of the potential neurobiological basis for comorbid schizophrenia and obsessive compulsive disorder, it is known that both involve serotonin and dopamine neurotransmitter systems, and that particular structures of the brain are implicated in both disorders, including prefrontal cortex, the anterior cingulate cortex, caudate nucleus, and thalamus.<sup>5,31</sup> More research is needed to elucidate further details.

Some authors argue that data which shows specific characteristics of psychopathology, treatment response and course of illness related to individuals with schizophrenia and OCD, may suggest an obsessive subtype of schizophrenia (“schizo-obsessive” subtype) rather than two comorbid conditions.<sup>5,31</sup>

Because of the high prevalence and far-reaching clinical consequences of comorbid OCD and OCS in schizophrenia, some recommend routine evaluation for OCS in schizophrenia patients.<sup>8</sup>

### **2.3.5. Schizophrenia and post-traumatic stress disorder**

Comorbidity of schizophrenia and PTSD have been conceptualised in some studies as PTSD with psychotic symptoms and in others as psychotic illness with comorbid PTSD. Clinically and in research, difficulties may arise in differentiating between these two conditions as there are similarities in some symptoms (e.g. hallucinations versus flashbacks) and both conditions share certain risk factors.<sup>32</sup> In both disorders, there is a distinction between positive symptoms, such as

hallucinations and flashbacks; and negative symptoms such as decreased emotional expression, social isolation and a feeling of detachment from others.<sup>5,32</sup>

Also, there is some controversy about whether psychosis itself- like the frightening experiences of delusions and hallucinations- or related experiences like hospitalisation and seclusion can count as trauma that leads to PTSD.<sup>5</sup>

The reported prevalence of PTSD in psychosis has ranged widely from 0-67%.<sup>5</sup> The pooled prevalence of PTSD in schizophrenia has been estimated at 12.4%.<sup>2</sup>

Risk factors that have been identified for PTSD in schizophrenia include female gender, substance use, repeated or ongoing traumatic experiences and early-life trauma.<sup>16</sup>

Buckley et al argue that high rates of PTSD may be mostly related to increased rates of early exposure to trauma or as a result of psychosis-related trauma.<sup>5</sup> Grubaugh et al suggest that a bidirectional relationship exists between trauma and serious mental illness, with psychiatric symptoms increasing risk of victimisation and this trauma then causing further psychiatric symptoms and impairment.<sup>33</sup>

Schizophrenia with comorbid PTSD has been associated with worse symptoms of psychopathology, increased service use<sup>5</sup>, higher rates of depression<sup>32</sup> and suicidality<sup>5</sup>, more positive symptoms, worse psychosocial functioning and quality of life.<sup>32</sup>

Data on neurobiological factors associated with PTSD in schizophrenia is lacking.<sup>5</sup> Both schizophrenia and PTSD have been associated with structural abnormalities in specific parts of the brain e.g. frontal lobe.<sup>34,35</sup> Differences in smooth pursuit eye movement deficits in schizophrenia compared to PTSD with psychotic symptoms may suggest differences in underlying neurobiology, but replication is needed.<sup>16</sup>

Other hypotheses include that dopamine hypofunction in patients with comorbid schizophrenia and PTSD may lead to increased firing of the locus ceruleus, more noradrenalin activity and

subsequent increase in levels of arousal.<sup>16</sup> Seedat et al have suggested that the exposure of neural networks to trauma (particularly the noradrenergic system and hypothalamic-pituitary axis), may cause susceptibility to both schizophrenia and PTSD.<sup>36</sup>

According to Buckley<sup>5</sup>, there have been no published genetic or family studies on PTSD in schizophrenia, and one twin study by Lyons et al showed no significant results.<sup>37</sup>

In terms of treatment, little consensus on appropriate pharmacological or non-pharmacological management of PTSD in psychotic illness has been reached so far.

## 2.4. Bipolar disorder and anxiety

As with schizophrenia, a high prevalence of anxiety disorders has been found in bipolar disorder and comorbid anxiety has been associated with worse outcomes.<sup>4</sup>

Two recent meta-analyses found similarly high prevalence rates of anxiety disorders in BPD, ranging from 42.7-45% lifetime prevalence.<sup>4,38</sup> The most common anxiety disorders co-occurring with BPD appear to be GAD (14.4-20%), SAD (13.3-20%), panic disorder (16.8-19%), PTSD (10.8-17%), OCD (10.7%), specific phobia (10.8%) and agoraphobia (7.8%).<sup>4,38</sup>

Comorbid anxiety disorders in bipolar disorder have been associated with increased suicidality, substance abuse, more mood episodes of increased severity, prolonged recovery time, poorer response to lithium, worse treatment side-effects, earlier age of onset of bipolar disorder, decreased quality of life, worse overall course of illness and impairment in functioning with continued functional impairment between mood episodes.<sup>4,38-43</sup>

Some suggested explanations for the high rate of comorbid anxiety disorders in bipolar disorder include common genetic susceptibility, common risk factors e.g. trauma or a stressful life event, the co-occurrence of anxiety symptoms with depressive episodes, or low self-esteem as another possible common factor.<sup>38</sup>

## 2.5.Schizoaffective disorder and anxiety

Few studies have looked at anxiety in SZA specifically. It has been included in some literature under the umbrella-term of schizophrenia-spectrum disorders. In others, comorbid anxiety disorders in SZA have been examined alongside other psychotic disorder diagnoses. Young et al estimates the prevalence of comorbid anxiety disorders in SZA to range from 32-45%.<sup>13</sup> In the same study, comorbid anxiety disorders were found to be more frequent in SZA than in BPD or schizophrenia. The authors proposed that this may be based on an association with affective symptoms found in SZA.

## 2.6.Substance-induced psychotic disorder and anxiety

Very little data were found regarding comorbidity of AD in substance-induced psychotic disorders. Only one study was identified which assessed 121 patients with methamphetamine-induced psychosis for anxiety symptoms.<sup>44</sup> This article reported 3.3% comorbidity with anxiety as measured by the Hamilton anxiety scale (HAM-A)<sup>45</sup> and 24.8% with OCD as measured by the Yale-Brown obsessive compulsive scale (Y-BOCS) .<sup>46</sup>

## 2.7.Treatment-emergent anxiety symptoms

Although anti-psychotic drugs can be used to treat anxiety disorders in patients without psychotic disorder<sup>16</sup>, these same medications appear to have the potential to worsen anxiety symptoms or even precipitate the onset of new anxiety symptoms in patients with psychotic illness.<sup>9,16</sup> This phenomenon seems to occur particularly during early phases of treatment, in younger patients, in males and in individuals with shorter duration of psychosis. Treatment-emergent social anxiety and obsessive compulsive symptoms appear to be associated with second-generation antipsychotics, particularly clozapine.<sup>9,16</sup>

## 2.8.Local literature

There is very little local data on anxiety in psychotic illness. Only three African studies were identified on the topic of anxiety in schizophrenia-spectrum disorders<sup>17,47,48</sup> and four others which focussed on comorbid OCS/OCD in psychotic illness.<sup>49-52</sup>

Emsley et al assessed a group of patients with schizophrenia/schizophreniform disorder for symptoms of depression and anxiety.<sup>53</sup> These were found to be lower than expected in comparison to previous literature. The authors hypothesised that this may have been because of the exclusion of schizoaffective disorder. In this study, depression and anxiety symptoms were more common in women, in first-episode psychosis and in patients with more positive psychotic symptoms.

A later South African study of anxiety in schizophrenia, assessed in-patients a week before discharge using a clinical interview, several diagnostic questionnaires and rating scales.<sup>17</sup> A total of 22.9% of this sample met diagnostic criteria for one or more anxiety disorder on the Mini International Neuropsychiatric Interview.<sup>54</sup> The most commonly diagnosed anxiety disorder was GAD (8.6%; n=6), followed by SAD (5.7%, n=4), OCD (4.3%, n=3) and PTSD (4.3%, n=3).

One other African study on comorbid anxiety disorders in patients with schizophrenia was found, from Nigeria.<sup>48</sup> This study used a larger sample (n=367) and found a lower prevalence overall, with the rate of anxiety disorders in their sample being 12.3%. The individual anxiety disorders measured were also slightly less prevalent, GAD having a 6.3% prevalence, OCD 3.3% and phobic anxiety disorder 2.7%.

Four African studies on OCD/OCS in psychotic illness were identified.<sup>49-52</sup> Three of these were South African and one Kenyan. The two South African studies that were not limited to Caucasian participants<sup>49,50</sup> (Xhosa speaking participants in Niehaus et al, participants of mixed ethnicity in Koen et al) found particularly low prevalence of OCD/OCS in SCZ. (0.5-1.1%). The South African study which was limited to Afrikaner participants<sup>55</sup>, as well as the Kenyan study<sup>52</sup>, found OCS/OCS rates more in keeping with international literature (12.2-13.2%). These authors hypothesise that certain ethnic or cultural factors may be protective against such comorbidity. An alternative explanation may be related to language and cultural factors affecting conceptual understanding and differentiating between obsessions and delusions.<sup>8</sup>

## 2.9. Conclusion

Comorbidity of anxiety disorders appears to be common, though under-recognised. Having an additional diagnosis of an anxiety disorder negatively affects prognosis and outcomes in a variety of

domains, as well as reducing quality of life. Although certain comorbidities have been examined more closely than others in the literature, there remains an overall lack of data on this clinically important topic. Understanding of the relationship between and neurobiological mechanisms underlying co-occurring anxiety and psychosis remains limited.

Various factors in research to date have caused heterogeneous data which is not easily comparable. In addition, diagnosis may be complicated in both clinical and research settings due to several factors.

Although some early data into possible pharmacological and psychotherapeutic treatment options exist, this is not yet adequate to inform clear clinical guidelines.

### **3. Limitations of the literature and motivation for this study**

Literature on anxiety disorders in psychotic illness remains deficient in many areas and generally heterogeneous. Particular areas that are lacking include longitudinal data which examine chronological relationships between anxiety, psychosis and psychotic prodrome, course of illness, response to treatment and outcomes. Further research into neurobiological mechanisms underlying the comorbid disorders may help to improve understanding of the psychopathology, inform future diagnostic categories and guide treatment approaches. Studies that compare comorbid anxiety disorders across psychotic diagnosis categories may aid in clarifying these specific relationships and focussing attention on the anxiety disorders that occur commonly in relation to a specific psychotic illness. Comorbidity of anxiety disorders in substance-induced psychotic disorders remains largely unexplored.

More randomised control trials are needed into drug management as well as further exploration of non-pharmacological interventions to establish what constitutes optimal management for this population. Development of more standardised instruments for screening and quantification of anxiety symptoms in psychosis may aid accurate diagnosis. More standardisation of sampling and other aspects of methodology in future studies will improve comparability and reduce the significant heterogeneity which is currently seen.

In the local context, there is a lack of South African data. More studies in South Africa are important because anxiety disorders have been found to be highly prevalent in the general population and may be affected by ethnic and cultural factors as well as high levels of violence and trauma in our society.

The aim of this study is to examine prevalence of anxiety disorders in psychotic illness in a local, South African context with specific focus on cross-diagnostic comparison and examination of potential socio-demographic correlates of this comorbidity. More data of this type may help to inform clinical practises including clinician-awareness, screening, accurate diagnosis and appropriate management which, in turn, will potentially affect outcomes for patients in this vulnerable population.

## 4. References

1. Bleuler, E. *Dementia Praecox or the Group of Schizophrenia*. (International University Press, 1911).
2. Achim, A. M. *et al.* How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophr. Bull.* **37**, 811–21 (2011).
3. Amerio, A. *et al.* The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review and meta-analysis. *J. Affect. Disord.* **186**, 99–109 (2015).
4. Nabavi, B., Mitchell, A. J. & Nutt, D. A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population. *EBioMedicine* **2**, 1405–19 (2015).
5. Buckley, P. F., Miller, B. J., Lehrer, D. S. & Castle, D. J. Psychiatric comorbidities and schizophrenia. *Schizophr. Bull.* **35**, 383–402 (2009).
6. Cunill, R., Castells, X. & Simeon, D. Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. *J. Clin. Psychiatry* **70**, 70–82 (2009).
7. Devulapalli, K. & Nasrallah, H. A. Schizophrenia and obsessive-compulsive disorder. *Am. J. Psychiatry* **167**, 1407–8 (2010).
8. Swets, M. *et al.* The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. *Schizophr. Res.* **152**, 458–468 (2014).
9. Temmingh, H. & Stein, D. J. Anxiety in Patients with Schizophrenia: Epidemiology and Management. *CNS Drugs* **29**, 819–32 (2015).
10. *Diagnostic and statistical manual of mental disorders IV-TR*. (American Psychiatric Association, 2000).
11. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. (American Psychiatric Publishing, 2013).
12. Pallanti, S., Cantisani, A. & Grassi, G. Anxiety as a core aspect of schizophrenia. *Curr. Psychiatry Rep.* **15**, 354 (2013).
13. Young, S. *et al.* Anxiety disorder comorbidity in bipolar disorder, schizophrenia and schizoaffective disorder. *Psychopathology* **46**, 176–85 (2013).
14. Cosoff, S. J. & Hafner, R. J. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Aust. N. Z. J. Psychiatry* **32**, 67–72 (1998).
15. Braga, R. J., Reynolds, G. P. & Siris, S. G. Anxiety comorbidity in schizophrenia. *Psychiatry Res.* **210**, 1–7 (2013).
16. Muller, J. E., Koen, L., Seedat, S., Emsley, R. A. & Stein, D. J. Anxiety disorders and schizophrenia. *Curr. Psychiatry Rep.* **6**, 255–261 (2004).
17. Seedat, S., Fritelli, V., Oosthuizen, P., Emsley, R. A. & Stein, D. J. Measuring anxiety in patients with schizophrenia. *J. Nerv. Ment. Dis.* **195**, 320–4 (2007).

18. First, M., Spitzer, R., Gibbon, M. & Williams, J. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version*. (Biometrics Research, New York State Psychiatric Institute, 2002).
19. Fonseka, T. M., Richter, M. A. & Müller, D. J. Second generation antipsychotic-induced obsessive-compulsive symptoms in schizophrenia: a review of the experimental literature. *Curr. Psychiatry Rep.* **16**, 510 (2014).
20. Yung, A. R. & McGorry, P. D. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr. Bull.* **22**, 353–70 (1996).
21. Woods, S. W. *et al.* Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr. Bull.* **35**, 894–908 (2009).
22. Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A. R. & McGuire, P. K. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr. Bull.* **40**, 120–31 (2014).
23. Pallanti, S., Quercioli, L. & Hollander, E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. *Am. J. Psychiatry* **161**, 53–8 (2004).
24. Berman, I. *et al.* Treatment of obsessive-compulsive symptoms in schizophrenic patients with clomipramine. *J. Clin. Psychopharmacol.* **15**, 206–10 (1995).
25. Sevincok, L., Akoglu, A. & Kokcu, F. Suicidality in schizophrenic patients with and without obsessive-compulsive disorder. *Schizophr. Res.* **90**, 198–202 (2007).
26. Rajkumar, R. P., Reddy, Y. C. J. & Kandavel, T. Clinical profile of ‘schizo-obsessive’ disorder: a comparative study. *Compr. Psychiatry* **49**, 262–8
27. Poyurovsky, M. *et al.* Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. *Compr. Psychiatry* **53**, 480–3 (2012).
28. de Haan, L., Sterk, B., Wouters, L. & Linszen, D. H. The 5-year course of obsessive-compulsive symptoms and obsessive-compulsive disorder in first-episode schizophrenia and related disorders. *Schizophr. Bull.* **39**, 151–60 (2013).
29. Cunill, R., Huerta-Ramos, E. & Castells, X. The effect of obsessive-compulsive symptomatology on executive functions in schizophrenia: a systematic review and meta-analysis. *Psychiatry Res.* **210**, 21–8 (2013).
30. Reznik, I. & Sirota, P. An open study of fluvoxamine augmentation of neuroleptics in schizophrenia with obsessive and compulsive symptoms. *Clin. Neuropharmacol.* **23**, 157–60
31. Poyurovsky, M., Weizman, A. & Weizman, R. Obsessive-compulsive disorder in schizophrenia: clinical characteristics and treatment. *CNS Drugs* **18**, 989–1010 (2004).
32. Seow, L. S. E. *et al.* A systematic review on comorbid post-traumatic stress disorder in schizophrenia. *Schizophr. Res.* (2016). doi:10.1016/j.schres.2016.05.004
33. Grubaugh, A. L., Zinzow, H. M., Paul, L., Egede, L. E. & Frueh, B. C. Trauma exposure and posttraumatic stress disorder in adults with severe mental illness: a critical review. *Clin. Psychol. Rev.* **31**, 883–99 (2011).
34. Shenton, M. E., Dickey, C. C., Frumin, M. & McCarley, R. W. A review of MRI findings in

- schizophrenia. *Schizophr. Res.* **49**, 1–52 (2001).
35. Karl, A. *et al.* A meta-analysis of structural brain abnormalities in PTSD. *Neurosci. Biobehav. Rev.* **30**, 1004–31 (2006).
  36. Seedat, S., Stein, M. B., Oosthuizen, P. P., Emsley, R. A. & Stein, D. J. Linking posttraumatic stress disorder and psychosis: a look at epidemiology, phenomenology, and treatment. *J. Nerv. Ment. Dis.* **191**, 675–81 (2003).
  37. Lyons, M. J. *et al.* Lifetime prevalence of mood and anxiety disorders in twin pairs discordant for schizophrenia. *Twin Res.* **3**, 28–32 (2000).
  38. Pavlova, B., Perlis, R. H., Alda, M. & Uher, R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. *The lancet. Psychiatry* **2**, 710–7 (2015).
  39. Angst, J. *et al.* Obsessive-compulsive syndromes and disorders: significance of comorbidity with bipolar and anxiety syndromes. *Eur. Arch. Psychiatry Clin. Neurosci.* **255**, 65–71 (2005).
  40. Simon, N. M. *et al.* Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. *J. Psychiatr. Res.* **37**, 187–92
  41. Lee, J. H. & Dunner, D. L. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. *Depress. Anxiety* **25**, 91–7 (2008).
  42. Toniolo, R. A., Caetano, S. C., da Silva, P. V. & Lafer, B. Clinical significance of lifetime panic disorder in the course of bipolar disorder type I. *Compr. Psychiatry* **50**, 9–12
  43. Otto, M. W. *et al.* Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. *Br. J. Psychiatry* **189**, 20–5 (2006).
  44. Eslami-Shahrbabaki, M., Fekrat, A. & Mazhari, S. A Study of the Prevalence of Psychiatric Disorders in Patients with Methamphetamine-Induced Psychosis. *Addict. Heal.* **7**, 37–46
  45. Maier, W., Buller, R., Philipp, M. & Heuser, I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. *J. Affect. Disord.* **14**, 61–8
  46. Goodman, W. K. *et al.* The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch. Gen. Psychiatry* **46**, 1006–11 (1989).
  47. Emsley, R. A., Oosthuizen, P. P., Joubert, A. F., Roberts, M. C. & Stein, D. J. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. *J. Clin. Psychiatry* **60**, 747–51 (1999).
  48. Aguocho, C., Aguocho, K., Uwakwe, R. & Onyema, G. Co-morbid anxiety disorders in patients with schizophrenia in a tertiary institution in South East Nigeria: prevalence and correlates. *Afr. Health Sci.* **15**, 137–45 (2015).
  49. Niehaus, D. J. H. *et al.* Obsessive compulsive disorder--prevalence in Xhosa-speaking schizophrenia patients. *S. Afr. Med. J.* **95**, 120–2 (2005).
  50. Koen, L. *et al.* Prevalence of obsessive compulsive disorder in first- and multi-episode male patients with schizophrenia-spectrum disorders. *S. Afr. Med. J.* **93**, 517–8 (2003).
  51. Seedat, F., Roos, J. L., Pretorius, H. W., Karayiorgou, M. & Nel, B. Prevalence and clinical

- characteristics of obsessive-compulsive disorder and obsessive compulsive symptoms in Afrikaner schizophrenia and schizoaffective disorder patients. *Afr. J. Psychiatry* **10**, 219–24 (2007).
52. Ndetei, D. M. *et al.* Obsessive-compulsive (oc) symptoms in psychiatric in-patients at Mathari hospital, Kenya. *Afr. J. Psychiatry* **11**, 182–6 (2008).
53. Emsley, R. A., Oosthuizen, P. P., Joubert, A. F., Roberts, M. C. & Stein, D. J. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. *J. Clin. Psychiatry* **60**, 747–51 (1999).
54. Sheehan, D. V *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 22-33-57 (1998).
55. Seedat, F., Roos, J. L., Pretorius, H. W., Karayiorgou, M. & Nel, B. Prevalence and clinical characteristics of obsessive-compulsive disorder and obsessive compulsive symptoms in Afrikaner schizophrenia and schizoaffective disorder patients. *Afr. J. Psychiatry* **10**, 219–24 (2007).

## **Chapter II: Publication-ready Manuscript**

### **Prevalence and correlates of anxiety disorders in psychotic illness**

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### **1. Introduction**

Symptoms of anxiety in psychotic illness have long been recognised and were even described by Bleuler.<sup>1,2</sup> Although there has been some recent increased interest in this topic, there is still a lack of data in this area and the studies that have been done vary widely in both methodology and outcomes, making analysis of results difficult.<sup>3-5</sup>

International data show a high prevalence of anxiety disorders (AD) in individuals with psychotic illnesses including schizophrenia (SCZ), schizoaffective disorder (SZA) and bipolar disorder (BPD).<sup>3,5,6</sup> One recent meta-analysis indicated that up to 38.3% of subjects with schizophrenia also suffered from at least one AD.<sup>3</sup> Social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) were the most common disorders. Literature on anxiety comorbidities in BPD also report high prevalence rates.<sup>5,6</sup>

In a study by Young et al, which included schizophrenia, bipolar disorder and schizoaffective disorder, high rates of anxiety disorders were found in all three psychotic disorder diagnoses.<sup>7</sup> The rates of AD were highest in the SZA group with a prevalence of 30.1%. In BPD and SCZ the rates were 22.4% and 16.7% respectively. A few small studies of patients with first episode psychosis and schizophreniform disorder have also shown high rates of anxiety symptoms, SAD and OCD.<sup>8-10</sup>

Very little data is available regarding the comorbidity of AD in substance-induced psychotic disorders. One study of 121 patients with methamphetamine-induced psychosis reported 3.3% comorbidity with anxiety as measured by the Hamilton anxiety scale (HAM-A)<sup>11</sup> and 24.8% with OCD as measured by the Yale-Brown obsessive compulsive scale<sup>12</sup> (Y-BOCS).<sup>13</sup>

In the local context, data is even sparser with only a few African and South African studies identified.<sup>8,10,14-18</sup> Some South African literature has found potentially lower rates of obsessive compulsive disorder in schizophrenia amongst non-Caucasian participants<sup>10,16</sup>, but these findings require replication and reasons for it remain unknown. With the known high prevalence of anxiety disorders amongst the general population in South Africa<sup>19</sup>, more local data on anxiety comorbidity in psychotic disorders is needed.

In the general population in South Africa, risk factors for anxiety disorders include female gender and lower educational levels.<sup>19</sup> In local and international data of anxiety within psychotic illnesses, higher prevalence has been noted amongst women and younger patients, but this data is limited.<sup>8,20,21</sup>

Accurate diagnosis in clinical practice and in research is often complicated due to overlapping symptom clusters and superficial similarities in presentation. In addition, both positive and negative symptoms of psychosis may mask anxiety as a result of the dramatic nature of positive symptoms and the effects of negative symptoms on emotional expressivity and communication.<sup>22</sup> Diagnosis may also be complicated by the hierarchical structure found in diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM).<sup>23,24</sup> Clinically, perhaps due to a combination of all these factors, anxiety disorders appear to be seldom recognised or treated in patients with psychotic illnesses.

Anxiety disorders themselves are disabling and can be potentially life threatening.<sup>7</sup> In addition, comorbid anxiety seems to have overall negative effects on outcomes of psychotic illness, including decreased levels of social functioning, worse quality of life, increased suicide risk, higher risk of relapse and poorer treatment response in psychotic illnesses.<sup>3,5,6,22,25,26</sup>

It remains unknown whether anxiety in psychotic illness should be viewed as secondary to the distressing nature of psychosis and related experiences, as a comorbidity that occurs by chance, as a result of shared risk factors or whether anxiety features represent part of a prodromal picture or different symptom dimension of the core condition.<sup>1</sup> A further complicating factor is that some neuroleptic drugs used in psychotic disorders have been associated with treatment-emergent anxiety symptoms.<sup>22,27-29</sup> As patterns of comorbidity are increasingly understood, these may give clues into underlying neurobiology of both anxiety and psychotic disorders.

Although not much is known about how best to treat comorbid anxiety in these populations, preliminary data has shown promising response to certain psychotherapeutic and pharmacological interventions.<sup>22,30-35</sup> Successful treatment of anxiety could potentially improve outcomes in individuals with psychotic illness and is particularly topical considering the increasing recognition of the heterogeneity of psychotic illness, the rise of the recovery movement and more interest in individualising management.

If more is known about the prevalence and correlates of AD in the various psychotic disorders, particularly in a South African context, clinical recognition, diagnosis and treatment of affected individuals may increase, ultimately improving outcomes.

The primary aim of this study was to investigate the prevalence and correlates of anxiety disorders in psychotic illness in a sample of patients from Valkenberg Hospital. We aimed to determine the overall prevalence of comorbid anxiety disorders in a sample of patients with psychotic disorder diagnoses and to measure the prevalence of anxiety disorders for each of the different psychotic disorder diagnoses and compare these. In addition, we aimed to test the hypothesis that comorbidity of AD in psychotic illness would correlate positively with female gender, younger age and a lower level of education.

Since collection of the data, the DSM-5 has been released, replacing the DSM-IV-TR. In DSM-5, OCD and PTSD were removed from the anxiety disorders chapter and selective mutism and separation anxiety were added. For the purposes of this study, the DSM-IV definition of anxiety disorders was utilised as the data was collected using SCID-I which includes OCD and PTSD as anxiety disorders but does not include selective mutism or separation anxiety.

## **2. Research methods and design**

### **2.1. Study design**

The study was a secondary analysis of an existing database. The original database was derived from a cross-sectional study investigating the psychobiology, presentation and risk factors in psychotic disorders, a pilot randomised trial of treatment partner interventions in people with serious mental illness and a neuroimaging study of psychotic disorders.

### **2.2. Study setting**

The sample of 226 participants represented in the database was selected from adult inpatients and outpatients attending Valkenberg Hospital in Cape Town, South Africa and referral centres in its catchment area.

Valkenberg Hospital is a state-funded psychiatric hospital which serves as a tertiary-level referral centre for the surrounding area of the Cape peninsula. The majority of the hospital's 340 beds are dedicated to acute psychiatric services for the admission of individuals with severe mental illness, often as involuntary patients. Both the hospital, and primary and secondary level healthcare facilities in its catchment area, provide various psychiatric outpatient services. Valkenberg Hospital is affiliated with the University of Cape Town's Department of Psychiatry and Mental Health, and functions as one of its main teaching hospitals.

### **2.3. Study population and sampling**

The sample of patients represented in the database, includes participants from three previous clinical studies. The first study randomly sampled inpatients from Valkenberg hospital. The second study recruited inpatients with severe mental disorders attending the same hospital as part of a randomised trial investigating a treatment partner and text messaging interventions to improve adherence. Inclusion criteria for these studies were patients with a diagnosis of a psychotic disorder, including bipolar disorder type I with psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder not otherwise specified, and substance induced psychotic disorders. The third neuroimaging study recruited only outpatients with psychotic disorders (schizophrenia, bipolar and methamphetamine psychosis) via advertisements and referral from clinicians from the same clinical setting. The age range for inclusion in all three studies was 18-65 years. Participants were

required to be able to speak conversational English. Patients with a diagnosis of dementia or psychosis due to general medical condition were excluded in all three primary studies. Data was collected from Jan 2009 to April 2014. All patients provided written informed consent to participate in the original studies. The original and secondary data analyses studies were approved by the Human Research Ethics Committee of the University of Cape Town.

Socio-demographic information was collected using a structured questionnaire. Clinical information and diagnosis was determined using the Structured Clinical Interview for DSM (SCID-I) <sup>36</sup>, Modules A,B,C,D,E,F. Module F records anxiety symptoms and generates diagnoses of the various DSM-IV defined anxiety disorders (Panic disorder, generalised anxiety disorder, OCD, PTSD, simple phobia, social phobia). Assessments were completed in English by psychiatrists and psychiatric nurses with extensive training and experience in SCID-I.

#### 2.4. Research procedure and data analysis

The relevant variables were extracted from the database and tabulated. We used Pearson's chi-squared test or Fisher's exact test where appropriate to analyse categorical data. We calculated the 95% confidence intervals around prevalence rates using the normal approximation of the binomial distribution. We used two-tailed test with a significance levels of  $p < 0.05$  throughout. Statistical analysis was carried out using Stata version 13 for Windows.

### **3. Results**

#### 3.1. Sample characteristics

The sample comprised 226 subjects, of whom 145 (64.16%) were male and 81 (35.84%) were female. The median age of the sample was 30, with a range between 18 and 61 years old. The majority of patients in the sample (179, 79.2%) had never been married, and most (n=155, 68.58%) were unemployed. Ethnicity of patients in the sample was categorised into "Coloured" (n=128, 56.64%), "African" (n=62, 27.43%), "Caucasian" (n=27, 11.95%) and "Other" (n=6, 2.65%). For three patients in the sample (1.33%), ethnicity was not captured. The highest level of education was between Grade 8 and Grade 11 for the majority of patients in the sample (n=112, 49.56%), with 34 (15.04%) having an educational level of Grade 7 or less, and 80 (35.4%) of Grade 12 or above.

Psychotic disorder diagnoses were divided into four categories: schizophrenia-spectrum, bipolar disorder, schizoaffective disorder and substance-induced mood or psychotic disorder. The schizophrenia-spectrum category comprised schizophrenia (n=106), schizophreniform disorder (n=5), psychotic disorder not otherwise specified (n=9) and brief psychotic disorder (n=1). This category totalled 121 patients, 53.54% of the sample. The bipolar disorder category (n=44, 19.47% of the sample) included only patients with bipolar disorder, type I with psychotic features. Schizoaffective disorder (n=30) comprised 13.27% of the total sample. The substance-induced mood or psychotic disorder category (n=31) was made up of substance-induced psychotic disorder (n=30) and substance-induced mood disorder (n=1) and constituted 13.72% of the sample.

### 3.2. Prevalence and correlates of anxiety disorders

The overall prevalence of any anxiety disorder in the entire sample was 14.6% (n=33), 95% CI [10.27-19.89%]. There was a significant association between psychotic disorder diagnosis and the presence of PTSD, with the schizoaffective disorder group having a higher rate of PTSD (13.3% vs. 3.3% in SCZ and 3.2% in SIMPD and 0% in BPD-I) (Fisher's exact test, p=0.039). In turn, there was a trend level association between psychotic disorder diagnosis and the presence of panic disorder (PD), with schizoaffective disorder patients having higher rates of PD (16.6% vs. 4.1% in SCZ spec, 3.2% in SIMPD and 2.2% in BPD\_I)(Fisher's exact test, p=0.052). (Table 1)

The most common anxiety disorder comorbidities were, in descending order, panic disorder (n=12, 5.31%; 95% CI [2.77-9.09%]), PTSD (n=9, 3.98%; 95% CI [1.84-7.42%]), specific phobia (n=7, 3.10%; 95% CI [1.25-6.28%]), anxiety disorder not otherwise specified (n=7, 3.10%; 95% CI [1.25-6.28%]), social phobia (n=4, 1.77%; 95% CI [0.48%-4.47%]), generalised anxiety disorder (n=4, 1.77%; 95% CI [0.48-4.47%]), substance-induced anxiety disorder (n=4, 1.77%; 95% CI [0.48-4.47%]) and obsessive compulsive disorder (n=2, 0.88%; 95% CI [0.11-3.16%]).

Associations of various sociodemographic variables with rates of comorbid anxiety disorders, were examined We found a significant association between level of education and the presence of PTSD, with higher rates of PTSD in patients with seven or less years of education (8.8%) compared to lower rates in those with 8-12 years of education (5.3%) and > 12years of education (0%)(Fisher's exact test, p=0.020). (Table 2)

**Table 1: Distribution of anxiety disorder comorbidity by psychotic disorder diagnosis**

	AAD	GAD	PD†	OCD	PTSD+	SIAD	Sp.P	AD NOS	SP
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Total sample</b>	33 (14.6)	4 (1.77)	12 (5.31)	2 (0.88)	9 (3.98)	4 (1.77)	7 (3.1)	7 (3.1)	4 (1.77)
<b>SCZ spec</b>	19 (15.7)	1 (0.83)	5 (4.13)	1 (0.83)	4 (3.31)	4 (3.31)	2 (1.65)	6 (4.96)	2 (1.65)
<b>BPD I</b>	7 (15.91)	2 (4.55)	1 (2.27)	0 (0)	0 (0)	0 (0)	1 (2.27)	1 (2.27)	2 (4.55)
<b>SZA</b>	6 (20)	1 (3.33)	5 (16.67)	1 (3.33)	4 (13.33)	0 (0)	3 (10)	0 (0)	0 (0)
<b>SIMPD</b>	1 (3.23)	0 (0)	1 (3.23)	0 (0)	1 (3.23)	0 (0)	1 (3.23)	0 (0)	0 (0)

\*Abbreviations: AAD=any anxiety disorder, GAD=generalised anxiety disorder, PD=panic disorder, OCD=obsessive compulsive disorder, PTSD= post-traumatic stress disorder, SIAD=substance-induced anxiety disorder, Sp.P=specific phobia, AD NOS=anxiety disorder not otherwise specified, SP=social phobia, SCZ spec=schizophrenia spectrum, BPD=bipolar disorder I, SZA=schizoaffective disorder, SIMPD=substance-induced mood/psychotic disorder.

† p=0.039, ‡ p= 0.052

\*\*Percentages calculated according to row totals for diagnostic category.

\*\*\*Some patients had more than one anxiety disorder diagnosis.

**Table 2: Comparison of sociodemographic characteristics of patients with psychotic disorder and comorbid anxiety disorder**

Demographic variable		AAD**	GAD	PD	OCD	PTSD†	AD NOS	Sp.P	SP	SIAD
Age in years	18-29	18 (16.07%*)	2 (1.79%)	7 (6.25%)	2 (1.79%)	6 (5.36%)	3 (2.68%)	3 (2.68%)	3 (2.68%)	3 (2.68%)
	30-44	13 (15.12%)	2 (2.33%)	4 (4.65%)	0 (0%)	2 (2.33%)	4 (4.65%)	4 (4.65%)	1 (1.16%)	1 (1.16%)
	45-65	2 (7.14%)	0 (0%)	1 (3.57%)	0 (0%)	1 (3.57%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender	M	21 (14.48%)	3 (2.07%)	7 (4.83%)	2 (1.38%)	5 (3.45%)	5 (3.45%)	2 (1.38%)	4 (2.76%)	3 (2.07%)
	F	12 (14.81%)	1 (1.23%)	5 (6.17%)	0 (0%)	4 (4.94%)	2 (2.47%)	5 (6.17%)	0 (0%)	1 (1.23%)
HLOE	<= Gr 7	5 (14.71%)	0 (0%)	2 (5.88%)	0 (0%)	3 (8.82%)	1 (2.94%)	1 (2.94%)	0 (0%)	0 (0%)
	Gr 8-11	19 (16.96%)	2 (1.79%)	8 (7.14%)	2 (1.79%)	6 (5.36%)	4 (3.57%)	6 (5.36%)	1 (0.89%)	3 (2.68%)
	Gr 12 +	9 (11.25%)	2 (2.50%)	2 (2.50%)	0 (0%)	0 (0%)	2 (2.50%)	0 (0%)	3 (3.75%)	1 (1.25%)
Marital status	Never married	28 (15.64%)	4 (2.23%)	9 (5.03%)	2 (1.12%)	6 (3.35%)	7 (3.91%)	5 (2.79%)	3 (1.68%)	4 (2.23%)
	Married or cohab.	3 (9.68%)	0 (0%)	2 (6.45%)	0 (0%)	1 (3.23%)	0 (0%)	1 (3.23%)	1 (3.23%)	0 (0%)
	Prev. married	2 (12.5%)	0 (0%)	1 (6.25%)	0 (0%)	2 (12.5%)	0 (0%)	1 (6.25%)	0 (0%)	0 (0%)
Employment	Empl.	13 (18.31%)	3 (4.23%)	4 (5.63%)	1 (1.41%)	1 (1.41%)	3 (4.23%)	2 (2.82%)	2 (2.82%)	1 (1.41%)
	Unempl.	20 (12.90%)	1 (0.65%)	8 (5.16%)	1 (0.65%)	8 (5.16%)	4 (2.58%)	5 (3.23%)	2 (1.29%)	3 (1.94%)
Ethnicity	Coloured	19 (14.84%)	2 (1.56%)	9 (7.03%)	0 (0%)	8 (6.25%)	3 (2.34%)	6 (4.69%)	1 (0.78%)	2 (1.56%)
	African	8 (12.90%)	1 (1.61%)	2 (3.23%)	1 (1.61%)	1 (1.61%)	3 (4.84%)	1 (1.61%)	1 (1.61%)	1 (1.61%)
	Caucasian	5 (18.52%)	1 (3.70%)	1 (3.70%)	1 (3.70%)	0 (0%)	1 (3.70%)	0 (0%)	1 (3.70%)	1 (3.70%)
	Other	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (16.67%)

\*\*Abbreviations: AAD=any anxiety disorder, GAD=generalised anxiety disorder, PD=panic disorder, OCD= obsessive compulsive disorder, PTSD= post-traumatic stress disorder, SAID=substance-induced anxiety disorder, Sp.P=specific phobia, AD NOS=anxiety disorder not otherwise specified, SP=social phobia, M=male, F=female, HLOE=highest level of education, Gr=grade, Prev.=previously, cohab.=cohabiting, Empl.=employed, Unempl.=unemployed.

\*Percentages calculated according to row variables.

† p= 0.020

\*\*\*Some patients had more than one anxiety disorder diagnosis, i.e each anxiety disorder category analysed separately

#### 4. Discussion

In this study of a sample of patients with psychotic disorders, we found an overall prevalence of anxiety disorders of 14.6%. This is lower than what has been reported in previous literature of comorbid anxiety disorders in psychotic illness but comparable to that reported by the South African Stress and Health (SASH) study, which showed a lifetime prevalence of anxiety disorders of 15.8% for the general population in South Africa.<sup>19</sup> Prevalence rates of individual anxiety disorders were also lower than previously published literature.

Possible reasons for the lower prevalence in this study include use of the SCID-I, which employs strict diagnostic hierarchy rules and has been associated with lower rates of anxiety comorbidity<sup>20</sup>, that the majority of the sample were inpatients and likely in the acute phase of a psychotic illness, and no use of self-report questionnaires or other additional, anxiety-specific diagnostic instruments. Another possible explanation is that of geographical and/or ethnic differences in South African patients with a psychotic disorder.

The most frequent comorbid anxiety disorders in our study were panic disorder and PTSD. This is out of keeping with other literature which has mostly found OCD and SAD to be the most common anxiety comorbidities in psychotic illness.

One possible reason for higher rates of PTSD may be related to the high levels of violence, crime and trauma in South Africa.<sup>37-40</sup> In addition, South Africa has a scarcity of health resources compared to first-world regions and this may have led to long periods of untreated psychosis, more exposure to trauma in the community while ill as well as in health-care settings e.g. over-crowded hospital wards increasing rates of assault.

Some previous literature from South Africa in non-Caucasian patients has shown lower rates of OCD in patients with schizophrenia.<sup>10,16</sup> It is unknown whether these differences are due to genetic, cultural or language differences or whether they represent problems of methodology e.g. problems in translation of rating scales. Considering that the majority of our sample was made up of non-Caucasian patients, the same factors may have affected our results, leading to a relatively low prevalence of OCD.

In terms of comparison across psychotic disorder diagnoses, we found a significant association between schizoaffective disorder and the prevalence of comorbid PTSD and PD. In a previous study which compared anxiety disorders in different psychotic illnesses, a similar association was found.<sup>7</sup> In this study, significant differences of comorbid anxiety were found between psychotic disorders, with the highest rate of anxiety disorders in schizoaffective disorder (30.1%), followed by BPD (22.4%) and then schizophrenia (16.7%). The authors hypothesised that higher prevalence of anxiety disorders in schizoaffective disorder may be associated with more mood features.

In assessment of previous literature, we hypothesised that comorbid anxiety disorders in psychotic illness may be associated with female gender, younger age and lower levels of education. We examined these as well as other socio-demographic variables in our statistical analyses. A significant association was found between prevalence of PTSD and less than eight years of education. This result is in keeping with findings from the SASH study which showed an association between anxiety disorders and an elementary level of education amongst the general population in South Africa.<sup>19</sup>

Certain results of this study differ from international literature and yet have commonalities with other South African studies. This raises the possibility of geographical differences in prevalence of comorbid anxiety disorders in psychotic illness. These differences may, in turn, support hypotheses relating such comorbidity to the effects of shared environmental risk factors. For example, higher rates of trauma exposure in the South African population is a likely factor in the higher prevalence of comorbid PTSD found in this study.

The lower prevalence rate of comorbid OCD is in keeping with other South African literature for non-Caucasian cohorts. This highlights potential effects of genetic or cultural factors that may be protective against OCD in psychotic illness. Further research in this area would be valuable in further elucidating this relationship and to identify what these factors may be.

Several limitations of this study need to be considered, due to it being a secondary analysis of an existing database.

Data was originally collected for studies with different hypotheses, aims and objectives to the current study. Additionally, the number of participants was determined by requirements of the original studies and may not represent an optimum sample size for the current study.

The exclusion of patients who were not able to converse in English as well as the administration of SCID-I in English may impact on the generalizability of the results.

A large proportion of participants included in the database were recruited as inpatients from a tertiary psychiatric facility. This sample may not be generalizable to other populations and may be skewed towards individuals with more severe forms of the relevant disorders or who were experiencing or recovering from an acute episode of illness at the time of the study.

Some correlations of anxiety in psychotic illness that have been described in the literature were not available for all participants in the current database. (E.g. history of childhood trauma, predominance of positive symptoms.) These factors were not examined in this study due to lack of the necessary data.

## **5. Conclusion**

Anxiety disorders have been shown to be a common comorbid problem for patients with psychotic illness and have negative effects on prognosis and outcome. Despite lower prevalence rates of comorbid anxiety disorders in our study, they remain a significant problem for some patients and have potentially far-reaching consequences.

The rate of clinically-recognised comorbid anxiety disorders is likely to be even lower than prevalence reported in research settings due to diagnostic difficulties and lack of clinician awareness. Although ideal treatment strategies remain unknown, some early data is available to guide management of such patients. Increased awareness, routine screening for anxiety symptoms and use of ratings scales and self-report instruments when appropriate, may increase clinical recognition and diagnosis rates, inform treatment choices and potentially improve outcomes for individuals with both anxiety and psychotic disorder.

Further research is needed, particularly in the South African setting and regarding appropriate treatment strategies.

## **6. Authors' contributions**

KR completed this project as a dissertation for the MMed degree at the University of Cape Town. PM was the primary supervisor, provided guidance in completing the project and assisted with related university procedures. HT was the co-supervisor, provided the raw data, developed the concept of the project and did the statistical data analysis. Both PM and HT assisted extensively with editing throughout the process.

## **7. Competing interests**

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

## 8. References

1. Buckley, P. F., Miller, B. J., Lehrer, D. S. & Castle, D. J. Psychiatric comorbidities and schizophrenia. *Schizophr. Bull.* **35**, 383–402 (2009).
2. Bleuler, E. *Dementia Praecox or the Group of Schizophrenia*. (International University Press, 1911).
3. Achim, A. M. *et al.* How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophr. Bull.* **37**, 811–21 (2011).
4. Amerio, A. *et al.* The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review and meta-analysis. *J. Affect. Disord.* **186**, 99–109 (2015).
5. Nabavi, B., Mitchell, A. J. & Nutt, D. A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population. *EBioMedicine* **2**, 1405–19 (2015).
6. Pavlova, B., Perlis, R. H., Alda, M. & Uher, R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. *The lancet. Psychiatry* **2**, 710–7 (2015).
7. Young, S. *et al.* Anxiety disorder comorbidity in bipolar disorder, schizophrenia and schizoaffective disorder. *Psychopathology* **46**, 176–85 (2013).
8. Emsley, R. A., Oosthuizen, P. P., Joubert, A. F., Roberts, M. C. & Stein, D. J. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. *J. Clin. Psychiatry* **60**, 747–51 (1999).
9. Michail, M. & Birchwood, M. Social anxiety disorder in first-episode psychosis: incidence, phenomenology and relationship with paranoia. *Br. J. Psychiatry* **195**, 234–41 (2009).
10. Koen, L. *et al.* Prevalence of obsessive compulsive disorder in first- and multi-episode male patients with schizophrenia-spectrum disorders. *S. Afr. Med. J.* **93**, 517–8 (2003).
11. Maier, W., Buller, R., Philipp, M. & Heuser, I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. *J. Affect. Disord.* **14**, 61–8
12. Goodman, W. K. *et al.* The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch. Gen. Psychiatry* **46**, 1006–11 (1989).
13. Eslami-Shahrbabaki, M., Fekrat, A. & Mazhari, S. A Study of the Prevalence of Psychiatric Disorders in Patients with Methamphetamine-Induced Psychosis. *Addict. Heal.* **7**, 37–46
14. Seedat, S., Fritelli, V., Oosthuizen, P., Emsley, R. A. & Stein, D. J. Measuring anxiety in patients with schizophrenia. *J. Nerv. Ment. Dis.* **195**, 320–4 (2007).
15. Seedat, F., Roos, J. L., Pretorius, H. W., Karayiorgou, M. & Nel, B. Prevalence and clinical characteristics of obsessive-compulsive disorder and obsessive compulsive symptoms in Afrikaner schizophrenia and schizoaffective disorder patients. *Afr. J. Psychiatry* **10**, 219–24 (2007).

16. Niehaus, D. J. H. *et al.* Obsessive compulsive disorder--prevalence in Xhosa-speaking schizophrenia patients. *S. Afr. Med. J.* **95**, 120–2 (2005).
17. Ndetei, D. M. *et al.* Obsessive-compulsive (oc) symptoms in psychiatric in-patients at Mathari hospital, Kenya. *Afr. J. Psychiatry* **11**, 182–6 (2008).
18. Aguocho, C., Aguocho, K., Uwakwe, R. & Onyeama, G. Co-morbid anxiety disorders in patients with schizophrenia in a tertiary institution in South East Nigeria: prevalence and correlates. *Afr. Health Sci.* **15**, 137–45 (2015).
19. Herman, A. A. *et al.* The South African Stress and Health (SASH) study: 12-month and lifetime prevalence of common mental disorders. *South African Med. J.* **99**, 339–344 (2009).
20. Achim, A. M. *et al.* How Prevalent Are Anxiety Disorders in Schizophrenia? A Meta-Analysis and Critical Review on a Significant Association. *Schizophr. Bull.* **37**, 811–821 (2011).
21. Vaswani, S. Schizophrenia with and without comorbid anxiety disorders. in *Paper presented at the 24th National Conference of the Anxiety Disorders Association of America* (2004).
22. Temmingh, H. & Stein, D. J. Anxiety in Patients with Schizophrenia: Epidemiology and Management. *CNS Drugs* **29**, 819–32 (2015).
23. *Diagnostic and statistical manual of mental disorders IV-TR.* (American Psychiatric Association, 2000).
24. *Diagnostic and statistical manual of mental disorders.* (American Psychiatric Association, 2013).
25. Muller, J. E., Koen, L., Seedat, S., Emsley, R. A. & Stein, D. J. Anxiety disorders and schizophrenia. *Curr. Psychiatry Rep.* **6**, 255–261 (2004).
26. Braga, R. J., Petrides, G. & Figueira, I. Anxiety disorders in schizophrenia. *Compr. Psychiatry* **45**, 460–468 (2004).
27. Cunill, R., Castells, X. & Simeon, D. Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. *J. Clin. Psychiatry* **70**, 70–82 (2009).
28. Devulapalli, K. & Nasrallah, H. A. Schizophrenia and obsessive-compulsive disorder. *Am. J. Psychiatry* **167**, 1407–8 (2010).
29. Swets, M. *et al.* The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. *Schizophr. Res.* **152**, 458–468 (2014).
30. Poyurovsky, M., Weizman, A. & Weizman, R. Obsessive-compulsive disorder in schizophrenia: clinical characteristics and treatment. *CNS Drugs* **18**, 989–1010 (2004).
31. Seedat, S., Stein, M. B., Oosthuizen, P. P., Emsley, R. A. & Stein, D. J. Linking posttraumatic stress disorder and psychosis: a look at epidemiology, phenomenology, and treatment. *J. Nerv. Ment. Dis.* **191**, 675–81 (2003).
32. Grubaugh, A. L., Zinzow, H. M., Paul, L., Egede, L. E. & Frueh, B. C. Trauma exposure and posttraumatic stress disorder in adults with severe mental illness: a critical review. *Clin. Psychol. Rev.* **31**, 883–99 (2011).
33. Rakofsky, J. J. & Dunlop, B. W. Treating nonspecific anxiety and anxiety disorders in patients

- with bipolar disorder: a review. *J. Clin. Psychiatry* **72**, 81–90 (2011).
34. Stratford, H. J., Cooper, M. J., Di Simplicio, M., Blackwell, S. E. & Holmes, E. A. Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review. *Clin. Psychol. Rev.* **35**, 19–34 (2015).
  35. Amerio, A., Odone, A., Marchesi, C. & Ghaemi, S. N. Treatment of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. *J. Affect. Disord.* **166**, 258–63 (2014).
  36. First, M., Spitzer, R., Gibbon, M. & Williams, J. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version*. (Biometrics Research, New York State Psychiatric Institute, 2002).
  37. Marais, A., de Villiers, P. J., Möller, A. T. & Stein, D. J. Domestic violence in patients visiting general practitioners--prevalence, phenomenology, and association with psychopathology. *S. Afr. Med. J.* **89**, 635–40 (1999).
  38. Peltzer, K. Traumatic experiencing and post traumatic psychological symptoms in South African University students. *Cent. Afr. J. Med.* **44**, 280–3 (1998).
  39. Peltzer, K. Posttraumatic stress symptoms in a population of rural children in South Africa. *Psychol. Rep.* **85**, 646–50 (1999).
  40. Seedat, S., Nyamai, C., Njenga, F., Vythilingum, B. & Stein, D. J. Trauma exposure and post-traumatic stress symptoms in urban African schools. Survey in CapeTown and Nairobi. *Br. J. Psychiatry* **184**, 169–75 (2004).

# Appendices

## 1. HREC approval



UNIVERSITY OF CAPE TOWN  
Faculty of Health Sciences  
Human Research Ethics Committee



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05 February 2016

**HREC REF: 034/2016**

**Dr P Milligan**  
Psychiatry & Mental Health  
Valkenberg Hospital

Dear Dr Milligan

**PROJECT TITLE: PREVALENCE AND CORRELATES OF ANXIETY DISORDERS IN PSYCHOTIC ILLNESS (MMed-candidate-Dr K Reid)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 28<sup>th</sup> February 2017.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

**We acknowledge that the following MMed student will also be involved in this study: Dr K Reid.**

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

**Signed**

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**  
Federal Wide Assurance Number: FWAD0001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 034/2016

## 2. South African Journal of Psychiatry: instructions to authors

### Overview

- **Original articles:** An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format (between 3000 and 4000 words with references kept to the minimum and being restricted to only the most relevant ones). Compulsory as a supplementary file: Ethical clearance letter/certificate.

Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis. [Read more.](#)

- **Literature review articles:** The review article presents a critical review of the literature on a topic that has both social and scientific value, and which is within the focus and scope of the journal (between 2500–4000 words with a maximum of 15 references). [Read more.](#)
- **Scientific Letter:** Original research that is limited in scope can be submitted as a scientific letter rather than a full original research article. A scientific letter should be no more than 1500 words, 6 references, and 1 table or figure. [Read more.](#)
- **Letters to the editor:** Should be about 400 words with only one illustration or table, and must include a correspondence address. They may be subjected to the peer review process and their eventual placement is at the discretion of the editorial team.
- **Obituaries:** Should be about 400 words and may be accompanied by a photograph.
- **Editorials:** Editorials are by invitation only and are intended to provide expert comment on relevant topics within the focus and scope of the journal. (Less than 800 words with a maximum of 10 references).

### General guidelines

When presenting your article in English. Please use British English, that is, according to the Oxford English Dictionary. Avoid Americanisms (e.g. use 's' and not 'z' spellings). Consult the Oxford English Dictionary when in doubt and remember to set your version of Microsoft Word to UK English.

- **Language:** Manuscripts must be written in British English.
- **Line numbers:** Insert continuous line numbers.
- **Font type:** Palatino
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- **General font size:** 12pt
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- **Headings:** Ensure that formatting for headings is consistent in the manuscript.
  - First headings: normal case, bold and 14pt
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- Our publication system supports a limited range of formats for text and graphics. Text files can be submitted in the following formats only:
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Your manuscript must adhere to the AOSIS house style. Refer to the [prepare manuscript](#) page.

## Original articles

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format (between 3000 and 4000 words with references kept to the minimum and being restricted to only the most relevant ones). Compulsory as a supplementary file: Ethical clearance letter/certificate.

Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

### Page 1

The format of the compulsory cover letter forms part of your submission and is on the first page of your manuscript and should always be in English. Refer to the [supporting documentation](#) page.

### Page 2 and onwards

#### Title

The article's full title should contain a maximum of 95 characters (including spaces).

#### Abstract

The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- **Background:** Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- **Aim:** State the overall aim of the study.
- **Setting:** State the setting for the study.
- **Methods:** Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- **Results:** State the main findings.
- **Conclusion:** State your conclusion and any key implications or recommendations. Do not cite references and do not use abbreviations excessively in the abstract.

The following headings serve as a guide for presenting your research in a well-structured original article. As an author you should include all first-level headings, but subsequent headings (second- and third-level headings) can be changed.

#### Introduction (first-level heading)

The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- **Social value:** The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- **Scientific value:** The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.

- **Conceptual framework:** In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- **Aim and objectives:** The introduction should conclude with a clear summary of the aim and objectives of this study.  
Research methods and design (first-level heading)

The methods should include:

- **Study design (second-level heading):** An outline of the type of study design.
- **Setting (second-level heading):** A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- **Study population and sampling strategy (second-level heading):** Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- **Intervention (if appropriate) (second-level heading):** If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- **Data collection (second-level heading):** Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- **Data analysis (second-level heading):** Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- **Ethical considerations (second-level heading):** Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.  
Results (first-level heading)

Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data.

All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

#### Discussion (first-level heading)

The discussion section should address the following four elements:

- **Key findings:** Summarise the key findings without reiterating details of the results.
- **Discussion of key findings:** Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- **Strengths and limitations:** Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- **Implications or recommendations:** State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

#### Conclusion (first-level heading)

Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

#### Acknowledgements (first-level heading)

If, through your study, you received any significant help in conceiving, designing or carrying out the work, or received materials from someone who did you a favour by supplying them, you must acknowledge their assistance and the service or material provided. Authors should always acknowledge outside reviewers of their drafts and any sources of funding that supported the research.

#### Competing interests (second-level heading)

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organisations that can potentially prevent you from executing and publishing unbiased research. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Where an author has no such competing interests, the listing will read as follows: 'The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.'

#### Authors' contributions (second-level heading)

This section is necessary to give appropriate credit to each author, and to the authors' applicable institution. The individual contributions of authors should be specified with their affiliation at the time of the study and completion of the work. An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. Contributions made by each of the authors listed can follow the example below (please note the use of authors' initials):

J.K. (University of Pretoria) was the project leader, L.M.N. (University of KwaZulu-Natal) and A.B. (Stellenbosch University) were responsible for experimental and project design. L.M.N. performed most of the experiments. P.R. (Cape Peninsula University of Technology) made conceptual contributions and S.T. (University of Cape Town), U.V. (University of Cape Town) and C.D. (University of Cape Town) performed some of the experiments. S.M. (Cape Peninsula University of Technology) and V.C. (Cape Peninsula University of Technology) prepared the samples and calculations were performed by C.S. (Cape Peninsula University of Technology).

#### References (first-level heading)

Begin the reference list on a separate page, and give no more than 15 references in all. Refer to the [prepare manuscript](#) page for the referencing style guidelines.