Comorbid Anxiety Disorders in Schizophrenia

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Abstract

Anxiety disorders commonly co-occur in patients of schizophrenia and have significant influence on course and prognosis of schizophrenia. However, probably due to diagnostic and treatment hierarchical reductionism anxiety disorders have been overlooked in schizophrenia. Review of the literature reveal great differences in prevalence estimates as a result of variations in symptom descriptions and different diagnostic instruments. There are significant differences in psychopathology of individuals with Schizophrenia with and without anxiety disorders. With regard to treatment response it is seen that subjects with Schizophrenia and anxiety disorders respond poorly to only antipsychotics but respond better to antipsychotics plus the SSRIs. Further, the duration of illness of schizophrenia subjects with anxiety disorder is comparatively briefer. The presence of comorbid anxiety disorder in schizophrenia patients may indicate a better prognosis. It is essential that schizophrenia patients undergo proper psychiatric screening and detailed evaluation to detect and treat comorbid anxiety disorders, since this may improve their quality of life and future prospects.

Keywords: Schizophrenia; anxiety disorders; prevalence; management.

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Introduction

In general medicine, Feinstein has defined comorbidity as, any separate and supplementary disorder that has coexisted or that may occur while the patient is suffering from the index disease under study. In recent times this expression is frequently used in clinical psychiatry to describe patients who receive a medical diagnosis in addition to their psychiatric disorder (e.g. major depression and hypertension), but much more frequently patients who are diagnosed with two or more psychiatric disorders.2 Dual diagnosis are associated with a number of undesirable sequels comprising higher dose and/or number of medicines, noncompliance, psychosocial problems, depression, deliberate self-harm, relapse, increased load on family and vagrancy. In addition, they often have

a poorer treatment outcome than those with a single diagnosis of a mental disorder.³

In the past two decades a number of studies have concluded that the co-occurrence of psychiatric disorders along with schizophrenia is frequent especially depression, substance abuse, anxiety disorders and obsessive-compulsive disorder (OCD).⁴⁻⁵ Despite these findings, there is paucity of well-planned studies in order to determine the prevalence and correlates of these co-morbid disorders. Furthermore, conclusive studies have not been done on the treatability of such conditions, although it is widely recognized that without comorbid schizophrenia these disorders are eminently treatable. Apart from all this, these co-morbid conditions may increase the infirmity of such patients as well. 6

In classical phenomenology, certain unusual

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mental experiences are objectified as psychiatric symptoms which in turn form the components of classification. However mental experiences may also be seen as stages in a psychopathological process. The role of affect in schizophrenia has recently been a focus of psychological accounts positive symptoms like hallucinations and delusions. Birchwood and Iqbal 7, have concentrated on depression, while Garety et al.8 believed in the centrality of anxiety, at the minimum in some patients. This group has studied the cognitive concomitants of anxiety: attentional biases; metacognitive processes like worry and views about the controllability of thoughts; Safety behaviors i.e. avoidance.9-11 Their findings imply that the intellectual procedures that accompany anxiety play a role in maintaining the symptoms of psychosis.9-11 Anxiety at the inception of insanity is fundamental to the neuropsychological explanation put forward by Gray et al., who implicated arousal in the development of delusions.¹²

It has been postulated that anxiety is a vital forerunner of schizophrenia. If this were true then a high prevalence of co-morbid anxiety disorders is expected in schizophrenia. The relationship can be established by studies either at the symptom level or at the level of diagnostic classes-both are potentially illuminating but unfortunately the psychiatric literature provides few references to a link between the symptoms of anxiety and schizophrenia as discussed earlier. This is despite the fact that various phenomenologists have been aware of the link. From early in the 20th century Eugen Bleuler described non psychotic abnormalities precede the commencement of schizophrenia. These were reported by him as well as others as anxiety, panic, depression, vague somatic complaints, obsessions and compulsions. 13

Fish also accepted that anxiety exists in individuals with schizophrenia. He believed that anxiety generally accompanied hallucinations and delusions of persecution during the acute phase of the illness. Conspicuous anxiety and depression was produced due to the abrupt inception of hallucinations . The patient with self-reference hallucinosis is usually very anxious and frightened. He therefore clearly saw anxiety arising secondary to the symptoms of the illness, though he also recognized that severe anxiety states might precede the inception of schizophrenic symptoms.14 Leonhard wrote about anxiety in relation to his concept of the cycloid psychoses. He named one variety the anxiety elation psychosis. He stated the basic disorder is a mood change of either anxiety

or ecstasy. Anxiety is associated with typical ideas of reference and sometimes with illusions and hallucinations. These paranoid symptoms are understood as arising from the mood. The pre psychotic personality is often anxious or hypomanic. He also has written about anxiety and other affective disorders sometimes occurring as accessory symptoms in the acute stage or systematic peripheries.¹⁵ In paranoid schizophrenia there is a morbid distortion of subject's beliefs or attitudes concerning relationship between themselves and other people. In chronic schizophrenia social withdrawal and emotional apathy are prominent features. Anxiety might therefore be specifically attached to other people in a way similar to the social anxiety syndromes. If this were so, one would certainly expect these disorders to be more prevalent in schizophrenia. On the other hand, nonsocial anxiety might lead to relatively more specific distortions in the capacity to evaluate the evidence in an objective way providing another potential route to distorted thinking.

Anxiety as a sign or as a disorder is common. Therefore its occurrence in subjects schizophrenia is expected. The association could be no more than chance. However, anxiety may have been already present in the individual who later developed schizophrenia. The cause of anxiety could be the same neurodevelopmental abnormality that results in schizophrenia. might also be secondary to distressing psychotic symptoms.16 In clinical practice however, the occurrence of anxiety disorders in schizophrenia is not very common. The reasons may be numerous. Clinicians often discount the presence of anxiety disorders in schizophrenia due to hierarchical considerations. The symptoms of anxiety disorders are attributed only to schizophrenia. Patients often conceal the syndromes due to shame. Symptoms of psychosis are intense and demand urgent action. In the presence of these symptoms minor signs of anxiety tend to be neglected. Additionally impaired cognitions and negative symptoms may interfere with the assessment of anxiety disorders in schizophrenia patients. Sometimes effects of antipsychotic medications may impede the identification of anxiety disorders in schizophrenia. Lastly few second generation antipsychotic drugs are reported to have precipitated symptoms of panic disorder (PD) 17 and social anxiety disorder. ¹⁸ Despite the clinical confounders, numerous recent studies have reported growing frequency of anxiety disorders in schizophrenia.4 6, 19-25 Thus to illuminate the problems in recognizing anxiety disorders in schizophrenia, the recent and past

literature was reviewed. First of all addressing the prevalence of anxiety disorders in schizophrenia, and then concentrating on the various correlates of such an association and lastly on those few treatment studies available for such conditions.

Comorbid anxiety and schizophrenia: earlier views:

Early observations on the co-occurrence of anxiety in patients with schizophrenia is found in some of the first observational studies. Eugen Bleuler's¹³ monograph and Kraeplin's ²⁶ Dementia Praecox and Paraphrenia, both describe commonly occurring and profound levels of anxiety in schizophrenia. Both discuss in particular, how often individuals with schizophrenia experience intense worry, over concern and panic, fearfully avoid others and are beset by a myriad of obsessions and compulsions. Particularly in the work of Bleuler, symptoms of anxiety are best described as commonly intervened with other more central schizophrenic symptoms and were noted to complicate the course of the disorder. In Bleuler's work, anxiety symptoms are associated with even greater withdrawal from social situations. Thus examination of Bleuler and Kraeplin's early works make it apparent that anxiety disorders have been identified in individuals with schizophrenia for nearly a century. In addition it has been posited that comorbid anxiety disorders may worsen the outcome of schizophrenia.

Prevalence of various anxiety disorders in schizophrenia

Boyd et al. conducted an epidemiological study in five US cities. All subjects were diagnosed using the NIMD- Diagnostic Interview Schedule (DIS). The prevalence of panic attacks was 37.9%. ²⁷ Different studies with clinical samples tried to evaluate the presence of comorbidities, principally concentrating on the different anxiety disorders. But due to the peculiarities inherent to the clinical samples and to the small sample size included in the studies, the results are highly variable and sometimes difficult to pool together.

Garvey et al., assessed ninety-five psychiatric inpatients for the coexisting anxiety disorders, out of which eighteen met the DSM-III criteria for schizophrenia. They reported that 44% of the individuals had comorbid anxiety disorder of which 17% had a current PD and 22% with generalized anxiety disorder. They also hypothesized that individuals with comorbid anxiety disorder possibly had a better prognosis.²⁸ Strakowski et al. studied one hundred and two acutely

psychotic, hospitalized first episode patients with ten having disorders in schizophrenia spectrum and found a rate of 6% for PD. They also said that comorbidity in schizophrenia was associated with longer hospitalization.²⁹ Sixty schizophrenia or schizoaffective disorder outpatients were randomly selected by Zarate et al. Out of which twenty-eight were with a comorbidity and thirty-two without a comorbidity. Of the patients having a comorbidity, 56.7% had a lifetime anxiety disorder, and 19.4% had PD. Also the individuals with comorbidity had poorer overall functioning.³⁰ Cassano et al. evaluated ninety-six consecutively hospitalized currently psychotic patients out of which ten had a diagnosis of schizophrenia as per the DSM-IV criteria and found a prevalence of 19.4% for PD in these patients. 19

Cosoff and Hafner, in sixty schizophrenia inpatients diagnosed using SCID DSM-III-R, identified 33% to have a comorbid anxiety disorder. The prevalence of the specific anxiety disorder was PD 5%, social phobia 17% and generalized anxiety disorder 12%. Although symptoms of psychiatric disorders were significantly higher in those with anxiety disorders on self-rating scales, hospital admissions rate were not. They also said that patients regularly admitted to hospital have elevated prevalence of anxiety disorders compared to those treated primarily in the community. ²⁰ But this was in contrast to what was found by Soni et al. who found higher levels of anxiety in patients who were managed in the community. ³¹

Bermanzohn et al. too found a prevalence rate of 40% of comorbid anxiety disorder in thirty-seven schizophrenic day care patients using the SCID-DSM-IV to find a prevalence of 29.7% for OCD and 10.8% for PD.²¹ Goodwin et al. while assessing 184 schizophrenic inpatients using DIGS, DSM-III-R found a prevalence of 42.5% for the anxiety disorder which constituted 5.4% of OCD patients, 7.1% with PD, 8.2% for agoraphobia as well as social phobia, 13.6% for the specific phobias.²²

While assessing thirty schizophrenic outpatients using MINI-DSM-IV, Tibbo et al. observed a rate of 26.7% (N=8) for generalized anxiety disorder, 23.3% (N=7) for social phobia, 6.6% (N=2) for PD with or without agoraphobia, 26.7% (N=8) for agoraphobia. These rates decreased when anxiety signs associated with symptoms of psychosis were excluded. Further they concluded that the comorbid anxiety disorders did not alter the outcome of schizophrenia in their study.²³ Pallanti et al. found a much higher prevalence rate of 60.2% using SCID DSM-IV in a group of eighty schizophrenic

outpatients. Out of which 36.3% were detected with social phobia, 22.5% with OCD, 13.8% with PD and a lower percentage of 3.8% with agoraphobia, 2.5% with specific phobia and generalized anxiety disorder each and a rate of 1.3% with PTSD. ⁶

While following a group of twenty-three schizophrenic out patients, Ciapparelli et al. found a prevalence of 47% for the comorbid anxiety disorders, which was quite similar to the most of the studies. It consisted of 40% of social phobia as well as PD and a rate of 20% for OCD and almost 33% of the patients received multiple anxiety diagnosis. Moreover patients with panic disorder and OCD showed greater severity of illness at baseline whereas patients with social anxiety disorder showed greater illness severity in remission.²⁵

Apart from the above studies there are several others which have frequently reported a high level of anxiety as a common symptom and a cause of disability in schizophrenic patients. It is frequently related to the positive symptoms of schizophrenia. So it is not taken into account as it has been established as a common symptom associated with schizophrenia. There are other studies which have concentrated on a single anxiety disorder comorbid with schizophrenic illness rather than focusing on the entire anxiety disorder spectrum. Of which most of them have concentrated on the epidemiology of PD and the rest of the disorders have obtained less attention. The following paragraphs will discuss about these studies.

Panic disorder in schizophrenia

Boyd reviewed the ECA data that included five large community samples (N=18,572). He observed the prevalence of panic attacks in individuals with schizophrenia varied from 28% to 63% in different communities. He specified panic attacks, not PD, and so the problem was more prevalent. Due to differences amongst DIS diagnosis and clinical diagnosis, he clearly mentioned that diagnoses were made as per DIS criteria and not DSM-III criteria.³² Tien and Eaton reexamined the ECA data and observed that individuals with panic attacks had increased odds (relative risk=2.28) of subsequently suffering from schizophrenia. This relation however, was not statistically significant (p=0.062). ³³

A Canadian community-based study also utilized the DIS instrument, also found that schizophrenia patients had an increased occurrence of PD. They also reported that onset of PD was prior to the onset of schizophrenia. ³⁴ Argyle reported that 7 (35%)

of twenty consecutive outpatients on maintenance treatment of schizophrenia complained of panic attacks that was occurring regularly. Four of the seven patients (18%) met the DSM III R criteria for PD, while three (15%) met the criteria for agoraphobia with panic attacks and one (5%) had agoraphobia without panic attacks.³⁵ After this Cutler and Siris interviewed a series of forty-five outpatients with schizophrenia and schizoaffective disorder with post psychotic depression and found panic attacks in eleven (25%) patients.³⁶

Bermanzohn et al. evaluating 37 chronic schizophrenia or schizo-affective disorder outpatients and found twelve (32.4%) had panic attacks, while eight (21.6%) had PD, five of whom also had agoraphobia. ³⁷ Another study included 60 schizophrenia or schizo-affective disorder patients. The authors reported PD in 8 (13%) patients, out of whom 5 (8%) had agoraphobia while 3 (5%) did not have agoraphobia. ³⁰

A prevalence rate of 43% (n=21) for PD was found by Labbate et al. in thirty outpatients of schizophrenia using the SCID DSM-IV diagnostic instrument. Out of which 33% had (n=16) PD currently of in the past. 38 On the other hand Bayle et al. in forty schizophrenia in and outpatients reported PD in 36.8%. Twelve of which were related to paranoid ideations.³⁹ Craig et al. found a low prevalence of 5% of PD using SCID DSM-III-R in two hundred twenty five of his patients suffering from schizophrenia and schizoaffective disorder, 14% of the patients had symptoms of PD.40 Ulas et al. evaluated 49 schizophrenia patients and observed that fifteen patients had suffered panic attacks during their illness, seven of which had a lifetime history of PD. 41

Social anxiety disorder in schizophrenia

Pilkonis et al. initially reported that schizophrenia patients had high social anxiety compared to controls.⁴² Penn et al. evaluated social anxiety in thirty eight schizophrenic patients by means of a battery of self-report measures of anxiety, a modified stroop task and an unstructured role play and found that the intensity of social anxiety was within the clinical range reported by pretreatment social phobic patients.⁴³ The full diagnosis of social phobia was first assessed in the Argyle study. They found social phobia in four (20%) of twenty consecutive schizophrenia patients on maintenance treatment.³⁵

Pallanti et al. evaluated eighty schizophrenia outpatients using SCID-DSM-IV-TR and found

Table 1. Frequency of Comorbid Anxiety Disorders in Schizophrenia.

First Author (Year)	Sample (size)	Diagnostic Instrument	PD	SP	GAD	Agora- phobia	Specific Phobia	AD NOS
Kessler (1994) [46]	National Co- morbidity survey	CIDI DSM-III-R	2.3%	7.9%	3.1%	2.8%	8.8%	-
Cosoff (1998) [20]	In-patients (60)	SCID DSM-III-R	5%	17%	12%	5%	5%	-
Bijl (1998) [47]	Netherlands Mental Health Survey and Incidence Study	CIDI DSM-III-R	2.2%	4.8%	1.2%	1.6%	7.1%	-
Labbate (1999) [38]	Out-patients (30)	SCID DSM-IV	43%	-	-	-	-	-
Henderson (2000) [48]	Australian adult population survey	CIDI ICD -10	1.3%	2.7%	9.7%	1.1%	-	-
Bermanzohn (2000) [21]	Day hospital (37)	SCID DSM-IV	10.8%	-	-	-	-	-
McConnell (2002) [49]	Out-patients (100)	SCAN ICD-10	2.4%	-	0.15%	0.7%	0.2%	-
Tibbo (2003) [23]	Out-patients (32)	MINI DSM-IV	3.3%	13.3%	16.7%	16.7%	-	-
Goodwin (2003) [22]	In-patients (184)	DIGS (SMIIIR)	7.1%†	8.2%	-	8.2%	13.6%	-
Pallanti (2004) [6]	Out-patients (80)	SCID DSM-IV	13.8%	36.3%	2.5%	3.8%	2.5%	-
Huppert (2005) [50]	Outpatients (32)	ADIS IV DSM IV	18.8%	37.5%	12.5%	-	-	-
Seedat (2007) [51]	Inpatients (70)	MINI DSM-IV	-	5.7%	8.6%	-	-	-
Nebioglu (2009) [52]	Out-patients (82)	SCID DSM-IV	8.5%	13.4%	8.5%	2.4%	9.7%	1.2%
Belene (2010) [53]	Out-patients (105)	SCID DSM-IV	4.76%	4.76%	NA	0.95%	14.28%	2.85%
Rapp (2012) [54]	Out-patients (255)	DIGS DSM IIIR	27.5%	-	-	-	-	-
Young (2013) [55]	Out-patients (174)	SCID DSMIV	6.9%	-	-	-	-	-
Aguocha (2015) [56]	Out-patients (367)	PSE 10ICD 10	NA	NA	6.3%	2.7%	NA	-
Nagargoje (2015) [57]	In & out-patients (60)	SCID DSM-IV	24.13%	31.3%	13.79%	NA	NA	NA
Lowengrub (2015) [58]	Outpatients (50)	SCID DSM-IV	NA	38%	-	-	-	-
Kiran (2016) [45]	Inpatients (93)	MINIICD 10	18.28%	9.68%	1.08%	6.45%	-	-
Vrbova (2017) [59]	Out-patients (61)	MINI ICD10	-	-	-	-	-	-
Bener (2018) [60]	Outpatients (396)	SCID5 DSM5	-	-	-	-	-	-
Aikawa (2018) [61]	Out-patients (207)	MINI DSM-IV	-	14.5%	-	-	-	-
Achim (2011) [88]	Meta-analysis		9.8%	14.9%	10.9%	5.4%	7.9%	

Abbreviations: PD: panic disorder; SP: social phobia; GAD: generalized anxiety disorder; ADNOS Anxiety disorder not otherwise specified; CIDI: Composite International Diagnostic interview; SCID: Structured Clinical Interview for Diagnosis; MINI: Mini International Neuropsychiatric Interview; DIGS: Diagnostic Interview for Genetic Studies; ADIS-IV: Anxiety Disorders Interview Schedule for DSM-IV

outpatients using SCID-DSM-IV-TR and found twenty-nine (36.3%) patients suffered from social anxiety disorder. [6] Mazeh et al. evaluated 117 patients with schizophrenia using DSM-IV SCID-P-Hebrew version and found that thirteen of them had a comorbid social phobia (11%). Higher severity PANSS total sore was associated with comorbid social phobia. Significant correlation was found between the scores of Leibowitz social anxiety scale fear and PANSS positive subscale. 44

Studies from India

Using a prospective, purposive sampling technique 93 inpatients of a tertiary care psychiatric hospital diagnosed as schizophrenia by ICD-10 DCR criteria and equal number of age and sex matched normal controls were evaluated for comorbid anxiety disorders. The prevalence of anxiety disorders in schizophrenia patients (35.48%) was significantly higher than in normal control subjects (16.12%).⁴⁵

Treatment of comorbid anxiety disorders in schizophrenia:
There is a lack of controlled studies evaluating

Table 2. Management of anxiety symptoms and comorbid anxiety disorders in schizophrenia

First author (Year)	Design, (sample size)			Outcomes			
Blin et al. (1996) [63]	Randomized trial Schizophrenia with Risperidone (N = 62) anxiety symptoms vs. haloperidol vs. methotrimeprazir			Significantly greater reductions in Psychotic Anxiety Scale in risperidone vs. methotrimeprazine group			
Kasper et al. (2004) [64]			Quetiapine	Significant reduction in BPRS anxiety/depression factor maintained over long-term tx			
Stern et al. (2009) [65]	Non-randomized, prospective trial (N = 16)	Schizophrenia, schizoaffective disorder with social anxiety symptoms	Aripiprazole (switched from existing antipsychotic to aripiprazole)	Significant reduction in LSAS, SDS			
Tollefson et al. (1999) [66]	Randomized trial, secondary analysis (N = 335)	Schizophrenia with anxiety symptoms	Olanzapine vs. PL; haloperidol vs. PL	Significantly greater reduction in BPRS anxiety depression factor in olanzapine (7.5–20 mg/day) vs. PL. No significant difference for haloperidol vs. PL groups			
Kanh (1988) [67]	Open trial (N=7)	Schizophrenia with panic disorder	Alprazolam	Clinical improvement on panic symptoms			
Argyle (1990) [35]	Case series (N=3)	Schizophrenia with panic attacks	Diazepam/alprazolam	Symptoms reduced			
Pallanti et al. (1999) [18]	Non-randomized, prospective trial (N = 12)	Schizophrenia with tx emergent social anxiety	Fluoxetine add-on to clozapine	Significant improvement in fear and anxiety subscore of LSAS			
Kiran (2018) [68]	Open label prospective study (N=33)	Schizophrenia with anxiety disorders	Fluoxetine add-on to antipsychotics	-			
Arlow (1997) [69]	Open trial (N=11)	Schizophrenia with panic disorder	CBT	Panic symptoms reduced in 7. Three patients decompensated			
Halperin (2000) [70]	Single blind, randomized study (N=20)	Schizophrenia with Social phobia	Group CBT for 8 weeks	Improvement of social anxiety and quality of life			
Kingsep (2003) [71]	Single blind, randomized study (N=30)	Schizophrenia with Social phobia	Group CBT for 12 weeks	Improvement of social anxiety and quality of life			

BPRS Brief Psychiatric Rating Scale, LSAS Liebowitz Social Anxiety Scale, OCD obsessive-compulsive disorder, OCS obsessive compulsive symptoms, PANSS Positive and Negative Syndrome Scale, PL placebo, pts patients, SDS Sheehan Disability Scale, SSRIs selective serotonin reuptake inhibitors, tx treatment, Y-BOCS Yale-Brown Obsessive-Compulsive Scale

twenty-nine (36.3%) patients suffered from social anxiety disorder.⁶ Mazeh et al. evaluated 117 patients with schizophrenia using DSM-IV SCID-P-Hebrew version and found that thirteen of them had a comorbid social phobia (11%). Higher severity PANSS total sore was associated with comorbid social phobia. Significant correlation was found between the scores of Leibowitz social anxiety scale fear and PANSS positive subscale.⁴⁴

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for comorbid anxiety disorders. The prevalence of anxiety disorders in schizophrenia patients (35.48%) was significantly higher than in normal control subjects (16.12%).⁴⁵

Treatment of comorbid anxiety disorders in schizophrenia:

There is a lack of controlled studies evaluating the management of panic symptoms in patients with schizophrenia. Anecdotal reports point to the fact that PD may be treated as usual in the presence of schizophrenia. One open prospective case series with alprazolam and case reports with alprazolam, diazepam, and imipramine consistently report improvement in panic symptoms.^{35,72} A case report has reported improvement in panic symptoms with the switch from haloperidol, bromperidol

and risperidone to quetiapine, which hadn't shown any improvement on fluoxamine,⁷³ and another had reported improvement with switch from haloperidol to risperidone.⁷⁴ Fer reports indicate that panic symptoms may worsen with long term use or increasing the dosages of antipsychotics. ⁷⁵ Eight patients with schizophrenia and comorbid PD underwent a 16 week clinical trial of cognitive behavioral group therapy. Results suggest that cognitive behavioral group therapy may be helpful in lessening symptoms. ⁷⁶ This was again confirmed by a study of four patients utilizing a cognitive behavioural intervention (panic control treatment) in 15-17 sessions with considerable improvement in both panic attacks and psychotic symptoms.⁷⁷

There is paucity of information regarding management of social phobia in schizophrenia. Two studies from Australia used cognitive behavioral group therapy for management of comorbid social anxiety in patients with schizophrenia.70-71 In one of them conducted by Halperin et al. patients were randomized to the treatment group or a waiting list group including 20 patients. The treatment which included exposure situation, cognitive restructuring and homework assignment in both groups was effective in improving measures of general psychopathology, social anxiety and quality of life after group CBT for a duration of 8weeks. In the other group the sessions took place for a duration of 12 weeks including 33 individuals. ⁷¹ Good evaluated the effect of CBT on psychotic symptoms in a schizophrenic patient suffering from social anxiety but no attempts were made to treat the psychotic symptoms per se, the scores for social phobia had decreased to a subclinical level over the course of treatment and also the psychotic symptoms rapidly abated. 78

The schizophrenia patients were evaluated for psychopathology and the presence of anxiety disorder at baseline. After being prescribed with antipsychotic medication in a suitable dose for 8 weeks, they were followed up at monthly intervals for the course of both schizophrenia and anxiety disorders. Thereafter, an selective serotonin reuptake inhibitor (SSRI) was also prescribed to the schizophrenia patients with comorbid anxiety disorder, and the patients were again followed up for a period of 8 weeks to assess the progress of schizophrenia and anxiety disorder Schizophrenia patients with anxiety disorder had a significantly higher positive score of the Positive and Negative Symptom Scale for Schizophrenia (PANSS) and a significantly lower score on the negative scale and the general psychopathology scale of the PANSS, as compared to the scores of the schizophrenia group without anxiety disorders. Schizophrenia patients with anxiety disorders responded well to the combination of SSRIs and antipsychotics but not antipsychotics alone. These anxiety disorders are quite responsive to the SSRIs but not to antipsychotics alone. Further, there is a shorter duration of illness in schizophrenia patients with anxiety disorders as compared to schizophrenia patients without anxiety disorders assigning a prognostic significance to the presence of comorbid anxiety disorders in schizophrenia.⁶⁸

Conclusion

The current review thus leads to the conclusion that patients with schizophrenia commonly have comorbid anxiety disorders. There is no significant association of these anxiety disorders and the basic psychopathology of schizophrenia. Schizophrenia patients with and without anxiety disorders show major differences in their symptomatology. The absolute reason for this is not known but the phenomenon most likely exists because of a common pathologic process or a common etiology. There is some evidence that subjects with schizophrenia and anxiety disorders have a shorter duration of illness compared to those without anxiety disorders. Comorbid anxiety disorders in schizophrenia respond well to treatment with SSRIs. Further the search for the causes of such an association might help in a better and more robust classification system for the proper placement of these disorders as well as the others.

References

- Feinstein, A.R. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970: 23: 455-68.
- 2. Pincus, H.A., Tew, D., First, M.B. Psychiatric comorbidity: is more or less? World Psychiatry, 2004; 3:18-23.
- 3. Drake, R.E., Mueser, K.T. Psychosocial approaches to dual diagnosis. Schizophrenia Bull 2000; 26:105-118.
- 4. Buckley, P.F., J., Lehrer, D.S., Castle, D.J. Psychiatric comorbidities and schizophrenia. Schizophrenia Bull 2008; 35(2): 383-402.
- McMillan, K.A., Enns, M.W., Cox, B.J., Sareen, J. Comorbidity of Axis I and II mental disorders with schizophrenia and psychotic disorders: findings from the national epidemiologic survey on alcohol and related conditions. Can J Psychiatry 2009; 54(7): 477–486.

- Pallanti, S., Quercioli, L., Hollander, E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. Am J Psychiatry, 2004; 161:53–58.
- 7. Birchwood, M., Iqbal, Z. Depression and suicidal thinking in psychosis: a cognitive approach. In: Wykes, T., Tarrier, N., Lewis, S. (eds). Outcome and innovation in psychological treatment of schizophrenia, Wiley, Chichester. 1998. pp 81–100.
- Garety, P., Kuipers, E., Fowler, D., Freeman, D., Bebbington, P. A cognitive model of the positive symptoms of psychosis. Psychol Med 2001; 31(2):189–195.
- 9. Freeman, D., Garety, P. Worry, worry processes and dimensions of delusions: an exploratory investigation of a role for anxiety processes in the maintenance of delusional distress. Behav Cog Psychother 1999; 27(1): 47–62.
- 10. Freeman, D., Garety, P. Cognitive therapy for an individual with a long-standing persecutory delusion: incorporating emotional processes into a multifactorial perspective on delusional beliefs. In: A. Morrison, (ed). From theory to practice. A casebook of cognitive therapy for psychosis. Chichester: Wiley. 2001. pp.121-143.
- 11. Freeman, D., Garety, P., Kuipers, E. Persecutory delusions: developing the understanding of belief, maintenance and emotional distress. Psychol Med 2001; 31(7): 1293-1306.
- Gray, J.A., Feldon, J., Rawlings, J.N., Hemsley, D.R., Smith, A.D. The neuropsychology of schizophrenia. Behav Brain Sc 1991;14(1):1–20.
- 13. Bleuler, E. Dementia praecox or the group of schizophrenias. Translated by J. Zinkin. New York: International Univesities Press. 1950.
- 14. Fish, F. Schizophrenia, 3rd ed. Hamilton, M. Williams & Wilkins, Baltimore.1984.
- Leonhard, K. The classification of endogenous psychoses. Translated from German by R. Berman., Irvington, New York. 1979.
- Davies, N., Russell, A., Jones, P., Murray, R.M. Which characteristics of schizophrenia predate psychosis? J Psychiatr Res 1998; 32(3):121–131.
- 17. Bressan, R.A., Monteiro, V.B., Dias, C.C. Panic disorder associated with clozapine. Am J Psychiatry 2000; 157:2056.
- Pallanti, S., Quercioli, L., Rossi, A., Pazzagli, A. The emergence of social phobia during Clozapine treatment and its response to Fluoxetine augmentation. Journal of Clinical Psychiatry, 1999; 60: 819-823.
- 19. Cassano, G.B., Pini, S., Saettoni, M., Rucci, P., Dell'Osso, L. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. J Clin Psychiat 1998; 59(2):60-68.

- Cosoff, S.J., Hafner, R.J. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. Australian and New Zealand Journal of Psychiatry, 1998; 32:67-72.
- 21. Bermanzohn, P.C., Porto, L., R.N.C., Arlow, P.B., Pollack, S., Stronger,R., Siris, S.G. Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. Schizophrenia Bull 2000; 26(3): 517-525.
- 22. Goodwin, R., Amador, X.F., Malaspina, D., Yale, S.A., Goetz, R.R., Gorman, J.M. Anxiety and substance use comorbidity among inpatients with schizophrenia. Schizophrenia Res 2003; 61:89-95.
- 23. Tibbo, P., Swainson, J., Chue, P., LeMelledo, J.M. Prevalence and relationship to delusions and hallucinations of anxiety disorders in schizophrenia. Depression and Anxiety, 2003; 17(2): 65-72.
- 24. Huppert, J.D., Smith, T.E. Anxiety and schizophrenia: the interaction of subtypes of anxiety and psychotic symptoms. CNS Spectrum, 2005; 10(9):721-31.
- Ciapparelli, A., Paggini, M., Marazziti, D., Carmassi, C., Bianchi, M., Taponecco, C., Consoli, G., Lombardi, V., Massimetti, G., Dell'Osso, L. Comorbidity with axis I anxiety disorders in remitted psychotic patients 1 year after hospitalization. CNS Spectrum, 2007; 12(12):913-919.
- 26. Kraeplin, E. Dementia Praecox and Paraphrenias. Translated by Barclay M. Bristol, England: Thoemmas Press. 2002.
- Boyd, J.H., Burke, J.D., Jr. Gruenberg, E. Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free syndromes. Arch Gen Psychiatry, 1984; 41: 983-989.
- Garvey, M., Noyes, R., Jr. Anderson, D., Cook, B. Examination of comorbid anxiety in psychiatric inpatients. Compr Psychiatry, 1991; 32: 465-473.
- 29. Strakowski, S.M., Tohen, M., Stoll, A.L., Faedda, G. L., Mayer, P.V., Kolbrener, M.L., Goodwin, D.C. Comorbidity in psychosis at first hospitalization. Am J Psychiatry, 1993; 150:752–757.
- Zarate, R., Kopelowicz, A., Mangano, R.G., Gonzalez, V., Ramirez, M. The comorbidity between schizophrenia and anxiety disorders. Paper presented at: 31st Annual Meeting of the Association for Advancement of Behavioral Therapy; November 13-16,1997. Miami Beach, Fla.
- 31. Soni, S.D., Mallik, A., Reed, P., Gaskell, K. Differences between chronic schizophrenic patients in the hospital and in the community.

- Hospital and Community Psychiatry, 1992; 43: 959-967.
- 32. Boyd, J.H. Use of mental health services for the treatment of panic disorder. Am J Psychiatry, 1986; 143: 1569-1574.
- Tien, A.Y., Eaton, W.W. Psychopathologic precursors and sociodemographic risk factors for the schizophrenia syndrome. Arch Gen Psychiatry, 1992; 49: 37-46.
- 34. Bland, R.C., Newman, S.C., Orn, H. Schizophrenia:Lifetime comorbidity in a community sample. Acta Psychiatr Scand 1987; 75: 383-391.
- 35. Argyle, N. Panic attacks in chronic schizophrenia. Br J Psychiatry, 1990; 157:430-3.
- Cutler, J.L., Siris, S.G. Panic-like symptomatology in schizophrenic and schizoaffective patients with postpsychotic depression: observations and implications. Compr Psychiatry, 1991; 32: 465-73.
- 37. Bermanzohn, P.C., Porto, L., Siris, S.G. Associated psychiatric syndromes (APS) in chronic schizophrenia. In: Proceedings of the 34th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 13, 1995.
- 38. Labbate, L.A., Young, P.C., Arana, G.W. Panic disorder in schizophrenia. Can J Psychiatry, 1999; 44: 488-490.
- 39. Bayle, F.J., Krebs, M.O., Epelbaum, C., Levy, D., Hardy, P. Clinical features of panic attacks in schizophrenia. European psychiatry, 2001; 16(6): 349-353.
- Craig, T., Hwang, M.Y., Bromet, E.J. Obsessivecompulsive and panic symptoms in patients with first-admission psychosis. Am J Psychiatry, 2002; 159: 592-8.
- 41. Ulas, H., Alptekin, K., Akdede, B.B., Tumuklu, M., Akvardar, Y., Kitis, A., Polat, S. Panic symptoms in schizophrenia: comorbidity and clinical correlates. Psychiatry & Clin Neurosc 2007; 61(6): 678-80.
- 42. Pilkonis PA, Feldman H, Himmelhoch J, Cornes C. (1980) Special anxiety and psychiatric diagnosis. J Nerv Ment Dis 1980; 160: 13-18
- 43. Penn, D.L., Hope, D.A., Spaulding, W., Kucera, J. Social anxiety in schizophrenia. Schizophrenia Research, 1994; 11 (3): 277–284.
- 44. Mazeh, D. Co-Morbid Social Phobia in Schizophrenia. Int J Soc Psychiatry, 2009; 55(3):198–202.
- 45. Kiran C, Chaudhury S. Prevalence of comorbid anxiety disorders in schizophrenia. Ind Psychiatry J 2016;25:35–40
- 46. Kessler R C, McGonagle K A, Zhao S, et al. Lifetime and 12-month prevalence of DSM-

- III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51: 8–19
- Bijl R, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998; 33: 587– 95
- Henderson S, Andrews G, Hall W. Australia's mental health: overview of the general population survey. Aust N Z J Psychiatry 2000; 34: 197–205.
- McConnell P, Bebbington P, McClelland R, et al. Prevalence of psychiatric disorder and the need for psychiatric care in Northern Ireland. Population study in the District of Derry. Br J Psychiatry 2002;181:214-9
- 50. Huppert J D, Smith TE. Anxiety and Schizophrenia: The Interaction of Subtypes of Anxiety and Psychotic Symptoms . CNS Spectrums 2005; 10(9): 721–731.
- 51. Seedat S, Fritelli V, Oosthuizen P, Emsley RA, Stein DJ. Measuring Anxiety in Patients with Schizophrenia. J Nerv Ment Dis 2007;195: 320–324
- Nebioglu M, Altindag A. The prevalence of comorbid anxiety disorders in outpatients with schizophrenia. Int J Psychiatry in Clin Pract, 2009; 13: 312–317
- 53. Belene E, Belene A, Algın F, Samancı A, Erkmen H. Comorbid Anxiety Disorders in Schizophrenia: The Relationship between Sociodemographic and Clinical Characteristics. J Psychiatry & Neurological Sc 2010;23:18–24
- 54. Rapp EK, Mandi White-Ajmani L, Antoniusb D, Goetz RR, Harkavy-Friedmand JM, Savitze AJ, Malaspina D, Kahn JP. Schizophrenia comorbid with panic disorder: Evidence for distinct cognitive profiles Psychiatry Res. 2012; 197(3): 206–211.
- 55. Young S, Pfaff D, Lewandowski KE, Ravichandran C, Cohen BM, Öngür D. Anxiety Disorder Comorbidity in Bipolar Disorder, Schizophrenia and Schizoaffective Disorder. Psychopathology. 2013;46(3):176–85.
- 56. Aguocha C, Aguocha K, Uwakwe R, Onyeama G. Co-morbid anxiety disorders in patients with schizophrenia in a tertiary institution in South East Nigeria: prevalence and correlates. African Health Sciences 2015; 15 (1): 137-45.
- 57. Nagargoje A K , Muthe M K. Prevalence of Anxiety in Schizophrenic Patients and its Impact on Quality of Life. International Journal of Scientific Study 2015; 3(7): 12–7.
- 58. Lowengrub K M, Stryjer R, Birger M, Lancu L. Social Anxiety Disorder Comorbid with

- Schizophrenia: The Importance of Screening for This Underrecognized and Undertreated Condition. Isr J Psychiatry Relat Sci 2015; 52 (1): 40–6
- Vrbova K, Prasko J, Ociskova M, Holubova M. Comorbidity of schizophrenia and social phobia - impact on quality of life, hope, and personality traits: a cross sectional study. Neuropsychiatr Dis Treat 2017;13: 2073–83
- Bener A, Dafeeah E E , Abou-Saleh M T , et al. Schizophrenia and co-morbid obsessive compulsive disorder: Clinical characteristics. Asian J Psychiatr. 2018; 37: 80-4
- Aikawa, S., Kobayashi, H., Nemoto, T., et al. M. Social anxiety and risk factors in patients with schizophrenia: Relationship with duration of untreated psychosis. Psychiatry Res 2018; 263:94–100.
- 62. Achim AM, Maziade M, Raymond E, Olivier D, Merette C, Roy MA. How Prevalent Are Anxiety Disorders in Schizophrenia? A Meta-Analysis and Critical Review on a Significant Association. Schizophrenia Bull 2011; 37 (4): 811–821.
- 63. Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. J Clin Psychopharmacol. 1996; 16(1): 38–44.
- 64. Kasper S. Quetiapine is effective against anxiety and depressive symptoms in long-term treatment of patients with schizophrenia. Depress Anxiety. 2004;20(1):44–7.
- 65. Stern RG, Petti TA, Bopp K, Tobia A. Aripiprazole for the treatment of schizophrenia with co-occurring social anxiety: an open-label cross-taper study. J Clin Psychopharmacol. 2009; 29(3):206–9.
- 66. Tollefson GD, Sanger TM. Anxious-depressive symptoms in schizophrenia: a new treatment target for pharmacotherapy? Schizophr Res. 1999;1(35 Suppl):S13–21.
- 67. Kahn JP, Puertollano MA, Schane MD, Klein DF. Adjunctive alprazolam for schizophrenia with panic anxiety: clin ical observation and pathogenetic implications. Am J Psychiatry 1988;145:742–744

- Kiran C, Chaudhury S. Correlates and management of comorbid anxiety disorders in schizophrenia. Ind Psychiatry J 2018; 27: 271-8.
- Arlow PB, Moran ME, Bermanzohn PC, Stronger R, Siris SG. Cognitive-behavioral treatment of panic attacks in chronic schizophrenia. J Psychother Pract Res 1997;6:145–150.
- Halperin S, Nathan P, Drummond P, Castle D. A cogni tive-behavioural, group-based intervention for social anxiety in schizophrenia. Aust NZ J Psychiatry 2000;34:809–813.
- Kingsep P, Nathan P, Castle D. Cognitive behavioural group treatment for social anxiety in schizophrenia. Schizophr Res 2003;63:121– 129.
- 72. Siris, S.G., Aaronson, A., Sellow, A.P. Imipramine responsive panic like symptomatology in schizophrenia. Biol Psychiatry, 1989; 25: 485–488.
- Takahashi, H., Sugita, T., Yoshida, K., Higuchi, H., Shimizu, T. Effect of Quetiapine in the Treatment of Panic Attacks in Patients with Schizophrenia: 3 Case Reports. J Neuropsychiatr Clin Neurosc, 2004; 16:113–115.
- Takahashi, H., Higuchi, H., Shimizu, H. Full remission of panic attacks in a schizophrenic patient after switching from haloperidol to risperidone. J Neuropsychiatr Clin Neurosc 2001; 13: 113–4.
- 75. Higuchi, H, Kamata, M, Yoshimoto, M, et al. Panic attacks in patients with chronic schizophrenia: A complication of long-term neuroleptic treatment. Psychiatr Clin Neurosc 2002; 53(1): 91– 94.
- 76. Arlow, P.B., Moran, M.E., Bermanzohn, P.C., et al. Cognitive-behavioral treatment of panic attacks in chronic schizophrenia. Schizophrenia Res 1997; 24(1-2): 219.
- Hofmann, S G., Bufka, L F., Brady, S M, et al. Cognitive-behavioral treatment of panic in patients with schizophrenia: preliminary findings. J Cogn Psychother, 2000; 14 (4):381– 392.
- 78. Good, J. The effect of treatment of a comorbid anxiety disorder on psychotic symptoms in a patient with a diagnosis of schizophrenia: a case study. Behav Cogn Psychotherapy, 2002; 30(3): 347.