ORIGINAL RESEARCH PAPER

Volume-7 | Issue-3 | March-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

AN OBSERVATIONAL STUDY OF CLINICAL PROFILE AND COGNITIVE INSIGHT IN PATIENTS OF TREATMENT RESISTANT SCHIZOPHRENIA

Psychiatry

Dr Kundan S. Kamble* MD, Assistant Professor, Department of Psychiatry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra. *Corresponding Author

Dr. Arun Kumar V DPM, DNB Assistant Professor, Department of Psychiatry, Government Medical College, Miraj, Maharashtra.

Dr Ajita S Nayak DPM, MD, Professor & Head of Unit, Department of Psychiatry, Seth GS Medical College & KEM Hospital, Mumbai, Maharashtra.

ABSTRACT

Objectives -It has been estimated that 20-50% patients with Schizophrenia can develop treatment resistance. Treatment resistance is associated with increased morbidity in these patients and it also increases the burden for the caretakers. Very few Indian studies have tried to establish the factors associated with resistance in Schizophrenia. Hence, this study was conducted to identify the socio-demographic profile, illness variables, co-morbidities and cognitive insight in patients with Treatment Resistant Schizophrenia.

Methodology: The study was conducted after permission from Institutional Ethics Committee. 50 consecutive patients of Treatment Resistant Schizophrenia (treated with 2 antipsychotics from different classes with adequate doses for 6 weeks each and currently satisfying the DSM IV TR criteria for Schizophrenia) were included in the study. Patients were administered a semi-structured questionnaire to obtain details about socio-demographic status, age of onset, family history, number of episodes and treatment received. DSM-IV-TR was used to identify psychiatric co-morbidities. Becks cognitive insight scale was used to assess cognitive insight.

Results: The mean age of patients in the study with Treatment Resistant Schizophrenia (TRS) was found to be 33.5yrs with M: F ratio of 1.77:1. It was found that 34% of patients had an onset before 20 yrs of age. Positive family history of mental illness was present in 48% of the TRS patients. Multiple episodes (>5) were present in 36% of patients. TRS was characterized by absence of affective symptoms in 90% of patients. On applying Beck's cognitive insight scale, patients of TRS were found to have higher Self-Certainty score as compared to Self-Reflection, indicating poor awareness into their illness and treatment.

Conclusions: It is important to identify Schizophrenia patients with early age of onset, positive family history, absence of affective features and poor cognitive insight to improve the long-term course of Schizophrenia.

KEYWORDS

Treatment Resistant Schizophrenia, Cognitive Insight

INTRODUCTION

Schizophrenia is a chronic disorder of body and mind that affects 5.5 per 1000 of the population.(Goldner, Hsu, Waraich, & Somers, 2002) The concept of Treatment Resistant Schizophrenia is best understood in the context of the diagnostic criteria for Schizophrenia being used, the definition of treatment response and the effectiveness of available treatments. The criteria most frequently used are the American Psychiatric Association's Practice guidelines for the treatment of patients with schizophrenia according to which "It can be defined based on little or no symptomatic response to multiple (at least 2) antipsychotic trials of an adequate duration (at least 6 weeks) and at a therapeutic dose range".(Fernandes, 2009) It has been estimated that cases of Treatment Resistant Schizophrenia can be 20-50% of the total. (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001; Elkis & Meltzer, 2007)

Various factors, studied in the past, have been suggested to be leading to poor response to treatment in patients with Schizophrenia. Epidemiological data revealed that male gender,(Meltzer, Rabinowitz, Lee, & Cola, 1997; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012) obstetric complications,(Alvir, Woerner, Gunduz, & Lieberman, 1997) absence of affective symptoms,(Kilzieh, Wood, Erdmann, Raskind, & Tapp, 2003; Rieckmann et al., 2005) early age of onset, (Meltzer et al., 1997; Vyas & Gogtay, 2012) positive family history, (Butzlaff & Hooley, 1998; Malaspina et al., 2000) severe and lengthy premorbid manifestation,(Bailer, Bräuer, & Rey, 1996; Wieselgren & Lindström, 1996) longer duration of untreated psychosis,(Edwards, Maude, McGorry, Harrigan, & Cocks, 1998; Lieberman et al., 1992) presence of soft neurological signs, early onset of abnormal involuntary movement and (Schulz, Conley, Kahn, & Alexander, 1989) low level of social functioning(Wiersma et al., 2000) were all associated with some degree of treatment refractoriness. However, very few Indian studies have tried to establish the predictors of outcome for Schizophrenia or find the risk factors associated with Treatment Resistant Schizophrenia.

Recently, a new concept about cognitive insight, was proposed by Beck et al. (2004; Pedrelli et al., 2004) Patients with Schizophrenia, especially deluded patients, were proposed to have a limited capacity for evaluation of their erroneous inferences and they seem to be relatively resistant to corrective feedback. Cognitive insight is concerned with distancing from and reassessing distorted beliefs and misinterpretations. Even though patients may accept an illness explanation for their symptoms and agree that this explanation makes sense (intellectual insight), still this may not produce any significant change in their underlying belief system (cognitive insight).(Beck & Debbie, 2004) Cognitive insight in Schizophrenia patients may be related to the current symptoms and stage of the illness.

Hence in this study, we aimed to study the socio-demographic profile, illness variables like age of onset, number of episodes, medical and psychiatric co–morbidities and cognitive insight in patients of Treatment Resistant Schizophrenia.

AIMS AND OBJECTIVES

1. To study the socio-demographic profile, illness variables, psychiatric and medical co-morbidities in patient with Treatment Resistant Schizophrenia.
2. To study the cognitive insight into illness and treatment in patient with Treatment Resistant Schizophrenia.

METHODOLOGY

This was an observational study done at a tertiary care hospital after Institutional Ethics Committee approval for the study, planned in accordance with the Declaration of Helsinki. 50 patients of Treatment Resistant Schizophrenia diagnosed in the Psychiatry OPD of a tertiary care hospital fulfilling the inclusion and exclusion criteria, and who gave consent, were selected for the study.

Inclusion criteria:

1] Age group: 18 to 50 yrs
2] Currently fulfilling the DSM IV TR criteria for Schizophrenia.
3] Treated by 2 antipsychotics from different classes with adequate doses for 6 weeks each.

Exclusion criteria:

1] Age: > 50 yrs and < 18 yrs
2] Non-compliant patients

PROCEDURE OF THE STUDY

50 patients with Treatment Resistant Schizophrenia attending the Psychiatric outpatient department fulfilling the inclusion and exclusion criteria were selected as cases. They were administered semi-structured questionnaires to obtain details about socio-demographic status, illness variables like age of onset, number of episodes, number of hospitalizations and medical co-morbidities. DSM-IV-TR was used to diagnose Schizophrenia and to identify the presence of affective features and psychiatric co-morbidities. Becks cognitive insight scale was used to assess insight.

MATERIALS

1) Semi-structured questionnaire for interview
It is designed to obtain details such as socio-demographic status, illness variables like number of episodes, number of hospitalizations, presence of affective features, suicidal ideation, drug addictions and medical co – morbidities.

2) Becks Cognitive Insight Scale:(Beck et al., 2004)
It Is a self-report inventory consisting of 15 statements, rated on a 4-point likert scale. Based on factor analyses, the scale is divided into 2 subscales. Self-reflectiveness subgroup consists of 9 items and self-certainty subgroup with 6 items. High score on subscale on self-reflectiveness and low scale on subscale of self-certainty considered as normal. A composite cognitive insight index score (Composite Index) is obtained by subtracting the self-certainty score from the self-reflectiveness.

3) Diagnostic and Statistical Manual of Mental Disorders – IV-TR criteria: (Association, 2000)

It is published by the American Psychiatric Association and provides a common language and standard criteria for the classification of mental disorders. A "Text Revision" of the DSM-IV, known as the DSM-IV-TR, was published in 2000. The diagnostic categories and the vast majority of the specific criteria for diagnosis were unchanged.

The Statistical Analysis was done using SPSS Software Version 17. Qualitative data were described with frequency and percentages. The Quantitative data were described as Mean and standard deviation.

RESULTS

In our study group, mean age was found to be 33.5yrs (±7.6) and 32 (64%) were found to be male. Majority of the sample consisted of secondary and higher level of education 40 (80%) and 29 (58%) were employed. Family history of Psychiatric illness was present in 24 (48%). The age of onset of illness was commonly between 21-30yrs of age i.e. 29 (58%) and most of the sample had <5 episodes of illness and hospitalisation. Only 10% (5) of the sample had presence of affective feature and of these majority were depressive 8%(4). Past suicidal ideation was present in 10 (20%). Drug addictions were found in 23 (46%) commonly nicotine was used and co-morbid surgical/ medical illness was present in 6 (12%). The details are shown in Table 1 & 2.

TABLE 1: Distribution of Sociodemographic in the sample (N=50)

S. No	Variables		Number	%
1.	Gender	Male	32	64
		Female	18	36
2.	Education	No schooling	1	2
		Primary	9	18
		Secondary	24	48
		Higher secondary	16	32
3	Family History	Present	24	48
		Absent	26	52
4	Age of onset	10-20 yrs.	17	34
		21-30	29	58
		31-40	4	8

TABLE 2: Distribution of illness variables in the sample (N= 50)

S. No	Variables		Number	%
1	No. of episodes	< 5 episodes	32	64
		≥ 5 episodes	18	36
2	No. of hospitalization	< 5 episodes	44	88
		≥ 5 episodes	6	12
3	Affective feature	Not present	45	90.0
		Depressive	4	8.0
		Grandiose	1	2.0
4	Suicidal ideation	Yes	10	20
		No	40	80
5	Drug addiction	Yes	23	46
		No	27	54
6	Medical/ surgical illness	Yes	6	12
		No	44	88

On applying the Becks Cognitive Insight Scale in patients of TRS we found that the mean Self-Reflectiveness score was 11.83 and the mean Self-Certainty score 12.88. Self-Reflectiveness items of the BCIS assess expression of introspection and the willingness to acknowledge fallibility (good insight) while the Self-Certainty items tap certainty about being right and resistance to correction (poor insight). Thus, our patients of TRS had poor awareness into their illness and treatment as indicated by a higher Self Certainty Score Compared to Self Reflection. The details are shown in Table 3.

Table 3: Distribution of Scores on BCIS (N=50)

BCIS	Mean	Standard Deviation
Composite index	-0.6	7.0

DISCUSSION

The mean age of the sample was found to be 33.5yrs and onset of illness was between 21-30yrs. This shows that onset of illness was in the early adult age and were found to be resistant within a period of 5-10yrs. Earlier studies have found association of early onset of illness (onset before adulthood) with premorbid developmental abnormalities, poor response to neuroleptic treatment, greater admission rates and poor prognosis. Studies have suggested the transition from Ultra Higr Risk group in the late adolescence to developing psychosis in the early adulthood affects the normal maturational process of grey and white matter regions at prefrontal cortex and superior temporal gyrus.(Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Glahn et al., 2008; Velakoulis et al., 2006; Yung et al., 2006)

In our study, males were found to be predominant with male-female ratio of 1.77:1. The male gender is an important risk factor of poor prognosis as they are associated with a poor response to neuroleptic treatment for chronic patients.(Leung & Psych, 2000; Meltzer et al., 1997; Szymanski, Lieberman, Alvir, & Mayerhoff, 1995) Women on the other hand have been reported to have increased sensitivity of dopamine receptors to dopamine antagonism of neuroleptics as the natural oestrogen has antidopaminergic effect.(Buckman & Peake, 1973)

In our study, more than half of the sample (58%) were employed. This finding was different from previous studies which have showed increased rate of unemployment in these patients. They have suggested that negative symptoms, poor premorbid function and cognitive dysfunction are significantly associated with unemployment in Schizophrenia. This difference in finding could be due to a better educational status of the patients in our sample. Most of them (80%) were secondary and above educated. Cognitive dysfunction, rather than clinical symptoms, could be the determining factor in the ability to work for patients with this disorder. Some previous studies have indicated that patients who were working full-time, were significantly better educated, more likely to be treatment-resistant, more likely to be treated with an atypical antipsychotic medication, had more positive symptoms, and were engaged in work tasks which were more cognitively complex than the part-time employed and unemployed work groups. Thus we did not find higher prevalence of uneducated or unemployed patients among our sample of Treatment Resistant Schizophrenia.(Marwaha & Johnson, 2004; Priebe, Warner, Hubschmid, & Eckle, 1998)

In our study, almost half the sample (48%) were found to have a family history of illness. This is higher compared to other patients of Schizophrenia.(Mortensen, Pedersen, & Pedersen, 2010) The greatest risk for developing Schizophrenia is having a first-degree relative with the disease (6.5%).(Kendler et al., 1993) The presence of family history of Schizophrenia has been found to be a poor prognostic factor.(Malaspina et al., 2000) Our findings also showed almost two third (64%) of the sample had <5 episodes of illness in the past. Lindenmayer et al have observed that non-responsive patients differed significantly in terms of higher number of illness episodes in comparison to responsive patients.(2000) Using parameters to define poor outcome, some authors employed the number of re-hospitalizations or chronic hospitalizations to define TRS but factors such as poor compliance, weak social support programs or a history of

violence can keep patients chronically hospitalized without having TRS. Our findings showed that 88% of the sample had <5 hospitalisations in the past. The rate of relapse is measured by evaluating the time from the last hospital discharge to the next hospitalization and the total number of hospitalizations per predetermined period. Few naturalistic follow-up studies have shown that up to one-half of all stabilized patients are readmitted to the hospital within 1 year after discharge.(Weiden, Aquila, & Standard, 1996) This high percentage is worrying since a high number of relapses is associated with disruption of the patient's life, poor long-term prognosis and high societal costs.(Sheitman, Lee, Strauss, & Lieberman, 1997)

Our study revealed that 90% of patient did not have affective symptoms which correlates with previous studies that affective symptom as good prognostic factor for Schizophrenia and less likely to be with TRS.(Jobe & Harrow, 2005)

In our study, suicidal ideation found in 20%. Other studies have found that almost half the patient had suicidal ideation in the past/present. In patients with Schizophrenia, suicide attempts were found to be 20-40%(Niskanen, Lonnqvist, & Achte, 1973; Planansky & Johnston, 1971) and complete suicide is 9-12.9%. (Allebeck, 1989; Newman & Bland, 1991)

Apart from this, 46% patients in our sample of TRS had a positive history of substance abuse and nicotine was the most common substance used. Studies in the past have found Schizophrenia patients use nicotine as a potential attempt to self-medicate and/or to partially counteract antipsychotic drug induced motor and cognitive side effects.(Kumari & Postma, 2005; Winterer, 2010). A study by Lasevoli et al found that nicotine use in TRS was associated with higher negative symptoms and was not significantly associated with better cognitive performances.(2013) Substances of abuse tend to increase dopaminergic activity, thereby increasing the risk of symptom exacerbation and relapse and compromising the efficacy of neuroleptic medication. Substance use is also thought to decrease compliance with treatment which leads to conflict in families, which can be detrimental to patients with Schizophrenia, who are highly vulnerable to heightened stress.(Bellack & Gearon, 1998)

In our study, we found 12% of the sample had a physical illness. Studies have reported that patient with severe mental illness like Schizophrenia are more prone to physical illness (Maj, 2009) and the increased prevalence of modifiable risk factors related to individual life style like smoking, Diabetes mellitus and obesity were the key factors for the illness. (Parks, Svendsen, Singer, Foti, & Mauer, 2006) Study by Koranyi et al found detection rate of physical illness among people with mental illness is very poor.(1979)

On applying the Becks Cognitive Insight Scale in patients of TRS, we found that the Self-Certainty score was more than Self-Reflectiveness score. This suggest that our patients had poor awareness into their illness and treatment. A lack of cognitive insight lead to impairment in both clinical insight and development of delusion.(Beck & Debbie, 2004) It may also lead such an individual to conclude that their interpretation (appraisals) of their experiences (e.g., 'there is a conspiracy against me') are factually correct contributing to the formation and maintenance of delusions.(Beck et al., 2004) Recent findings have highlighted the potential importance of cognitive insight as a mediator of response to cognitive behavioural therapy for psychosis,(Granholm et al., 2005) with increase in cognitive insight associated with reductions in positive, negative and general symptomatology.(Granholm, Auslander, Gottlieb, McQuaid, & McClure, 2006)

CONCLUSION

The mean age of patients with Treatment Resistant Schizophrenia was found to be 33.5yrs with a Male: Female ratio of 1.77:1, Majority of patients had received secondary education (48%) and were employed (58 %), 34% of patients were found to have early age of onset which is <20 yrs, 48% had a positive family history of mental illness, ≥ 5 number of episodes and hospitalisation were present in 36% and 12 % of TRS patients respectively. 90% of patients did not have affective symptoms and suicidal ideation was present in 20% of TRS patients. Patients of TRS have higher Self Certainty Score compared to Self-Reflection on BCIS indicating poor awareness into their illness and treatment.

CLINICAL IMPLICATION -

Management of treatment resistant patients has remained a persistent public health problem. It is important to identify Schizophrenia patients with risk factors like early age of onset, family history and absence of affective features which can lead to poor outcome. Early detection of these risk factors can improve the long-term course of TRS. Interventions in the form of cognitive behaviour therapy to improve cognitive insight in these patients need to be instituted.

Reference:

1. Allebeck, P. (1989). Schizophrenia: a life-shortening disease. Schizophrenia Bulletin, 15(1), 81.
2. Alvir, J. M. J., Woerner, M. G., Gunduz, H., & Lieberman, J. A. (1997). 579-Obstetric complications predict treatment response in first episode schizophrenia. Schizophrenia Research, 24(1), 204–205.
3. Association, A. P. (2000). Diagnostic and Statistical Manual of Mental Disorders (Text Revision). Arlington, VA: American Psychiatrie Association.
4. Bailer, J., Bräuer, W., & Rey, E.-R. (1996). Premorbid adjustment as predictor of outcome in schizophrenia: results of a prospective study. Acta Psychiatrica Scandinavica, 93(5), 368–377.
5. Beck, A. T., Baruch, E., Balter, J. M., Steer, R. A., & Warman, D. M. (2004). A new instrument for measuring insight: the Beck Cognitive Insight Scale. Schizophrenia Research, 68(2), 319–329.
6. Beck, A. T., & Debbie, M. (2004). Cognitive insight: theory and assessment.
7. Bellack, A. S., & Gearon, J. S. (1998). Substance abuse treatment for people with schizophrenia. Addictive Behaviors, 23(6), 749–766.
8. Buckman, M. T., & Peake, G. T. (1973). Estrogen potentiation of phenothiazine-induced prolactin secretion in man. The Journal of Clinical Endocrinology & Metabolism, 37(6), 977–980.
9. Butzlaff, R. L., & Hooley, J. M. (1998). Expressed emotion and psychiatric relapse: a meta-analysis. Archives of General Psychiatry, 55(6), 547–552.
10. Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., & Sheitman, B. (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. American Journal of Psychiatry, 158(4), 518–526.
11. Edwards, J., Maude, D., McGorry, P. D., Harrigan, S. M., & Cocks, J. T. (1998). Prolonged recovery in first-episode psychosis. The British Journal of Psychiatry.
12. Elkis, H., & Meltzer, H. Y. (2007). Refractory schizophrenia. Revista Brasileira de Psiquiatria, 29, S41–S47.
13. Fernandes, J. (2009). American Psychiatric Association–DSM-IV-TR-Manual de diagnóstico e estatística das perturbações mentais. Quarta edição.
14. Fornito, A., Yücel, M., Patti, J., Wood, S. J., & Pantelis, C. (2009). Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophrenia Research, 108(1), 104–113.
15. Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., … Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biological Psychiatry, 64(9), 774–781.
16. Goldner, E. M., Hsu, L., Waraich, P., & Somers, J. M. (2002). Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. The Canadian Journal of Psychiatry, 47(9), 833–843.
17. Granholm, E., Auslander, L. A., Gottlieb, J. D., McQuaid, J. R., & McClure, F. S. (2006). Therapeutic factors contributing to change in cognitive-behavioral group therapy for older persons with schizophrenia. Journal of Contemporary Psychotherapy, 36(1), 31.
18. Granholm, E., McQuaid, J. R., McClure, F. S., Auslander, L. A., Perivoliotis, D., Pedrelli, P., … Jeste, D. V. (2005). A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. American Journal of Psychiatry, 162(3), 520–529.
19. Iasevoli, F., Balletta, R., Gilardi, V., Giordano, S., & De Bartolomeis, A. (2013). Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. Neuropsychiatric Disease and Treatment, 9, 1113.
20. Jobe, T. H., & Harrow, M. (2005). Long-term outcome of patients with schizophrenia: a review. The Canadian Journal of Psychiatry, 50(14), 892–900.
21. Kendler, K. S., McGuire, M., Gruenberg, A. M., O'hare, A., Spellman, M., & Walsh, D. (1993). The Roscommon family study: I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. Archives of General Psychiatry, 50(7), 527–540.
22. Kilzieh, N., Wood, A. E., Erdmann, J., Raskind, M., & Tapp, A. (2003). Depression in Kraepelinian schizophrenia. Comprehensive Psychiatry, 44(1), 1–6.
23. Koranyi, E. K. (1979). Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Archives of General Psychiatry, 36(4), 414–419.
24. Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: the self medication hypotheses. Neuroscience & Biobehavioral Reviews, 29(6), 1021–1034.
25. Leung, M. D., & Psych, C. M. (2000). Sex differences in schizophrenia, a review of the literature. Acta Psychiatrica Scandinavica, 101(401), 3–38.
26. Lieberman, J. A., Alvir, J. M. J., Woerner, M., Degreef, G., Bilder, R. M., Ashtari, M., … Loebel, A. (1992). Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. Schizophrenia Bulletin, 18(3), 351.
27. Lindenmayer, J.-P. (2000). Treatment refractory schizophrenia. Psychiatric Quarterly, 71(4), 373–384.
28. Maj, M. (2009). Physical health care in persons with severe mental illness: a public health and ethical priority. World Psychiatry, 8(1), 1–2.
29. Malaspina, D., Goetz, R. R., Yale, S., Berman, A., Friedman, J. H., Tremeau, F., … Brown, A. (2000). Relation of familial schizophrenia to negative symptoms but not to the deficit syndrome. American Journal of Psychiatry, 157(6), 994–1003.
30. Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment. Social Psychiatry and Psychiatric Epidemiology, 39(5), 337–349.
31. Meltzer, H. Y., Rabinowitz, J., Lee, M. A., & Cola, P. A. (1997). Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. The American Journal of Psychiatry, 154(4), 475.
32. Mortensen, P. B., Pedersen, M. G., & Pedersen, C. B. (2010). Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? Psychological Medicine, 40(2), 201–210.
33. Newman, S. C., & Bland, R. C. (1991). Mortality in a cohort of patients with schizophrenia: a record linkage study. The Canadian Journal of Psychiatry, 36(4), 239–245.
34. Niskanen, P., Lonnqvist, J., & Achte, K. A. (1973). Schizophrenia and suicides. Psychiatria Fennica.
35. Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophrenia Research and Treatment, 2012.
36. Parks, J., Svendsen, D., Singer, P., Foti, M. E., & Mauer, B. (2006). Morbidity and mortality in people with serious mental illness. Alexandria, VA: National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council,

25(4).
37. Pedrelli, P., McQuaid, J. R., Granholm, E., Patterson, T. L., McClure, F., Beck, A. T., & Jeste, D. V. (2004). Measuring cognitive insight in middle-aged and older patients with psychotic disorders. Schizophrenia Research, 71(2), 297–305.
38. Planansky, K., & Johnston, R. (1971). The occurrence and characteristics of suicidal preoccupation and acts in schizophrenia. Acta Psychiatrica Scandinavica, 47(4), 473–483.
39. Priebe, S., Warner, R., Hubschmid, T., & Eckle, I. (1998). Employment, attitudes toward work, and quality of life among people with schizophrenia in three countries. Schizophrenia Bulletin, 24(3), 469–477.
40. Rieckmann, N., Reichenberg, A., Bowie, C. R., Parrella, M., White, L., Friedman, J. I., & Harvey, P. D. (2005). Depressed mood and its functional correlates in institutionalized schizophrenia patients. Schizophrenia Research, 77(2), 179–187.
41. Schulz, S. C., Conley, R. R., Kahn, E. M., & Alexander, J. (1989). Nonresponders to neuroleptics: a distinct subtype. Oxford University Press, New York.
42. Sheitman, B. B., Lee, H., Strauss, R., & Lieberman, J. A. (1997). The evaluation and treatment of first-episode psychosis. Schizophrenia Bulletin, 23(4), 653.
43. Szymanski, S., Lieberman, J. A., Alvir, J. M., & Mayerhoff, D. (1995). Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. The American Journal of Psychiatry, 152(5), 698.
44. Velakoulis, D., Wood, S. J., Wong, M. T., McGorry, P. D., Yung, A., Phillips, L., … Desmond, P. (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: A magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra–high-risk individuals. Archives of General Psychiatry, 63(2), 139–149.
45. Vyas, N. S., & Gogtay, N. (2012). Treatment of early onset schizophrenia: recent trends, challenges and future considerations. Frontiers in Psychiatry, 3.
46. Weiden, P., Aquila, R., & Standard, J. (1996). Atypical antipsychotic drugs and long-term outcome of schizophrenia. Journal of Clinical Psychiatry, 57(11), 53–60.
47. Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., Der Heiden, W. A., … Walsh, D. (2000). Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. Psychological Medicine, 30(5), 1155–1167.
48. Wieselgren, I.-M., & Lindström, L. H. (1996). A prospective 1–5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. Acta Psychiatrica Scandinavica, 93(1), 9–19.
49. Winterer, G. (2010). Why do patients with schizophrenia smoke?. Current Opinion in Psychiatry, 23(2), 112–119.
50. Yung, A. R., Stanford, C., Cosgrave, E., Killackey, E., Phillips, L., Nelson, B., & McGorry, P. D. (2006). Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. Schizophrenia Research, 84(1), 57–66.