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An overview about Insomnia and Suicide in Schizophrenia

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Abstract: Insomnia is a common comorbid condition in patients with schizophrenia. Accumulating evidence has suggested that sleep disturbance can be a risk factor for, or a prodromal symptom of psychosis; it can also aggravate psychotic symptoms, therefore interfering with the treatment of schizophrenia. Symptoms related to disordered sleep, including reduced sleep time and quality of sleep, often go untreated and persist as chronic, clinically significant insomnia. Notably, observed abnormalities in these polysomnographic traits have been shown to be heritable, thus further strengthening the argument for an etiological link between insomnia and schizophrenia. Clinical interest in this relationship has grown with the understanding that the presence of sleep disturbance, especially clinically significant insomnia, corresponds with reduced quality of life (QOL) and likely worse clinical outcomes for patients with schizophrenia. Recent studies have found that the increased risk for suicidal behavior in schizophrenia is associated with the unemployment, a family history of psychiatric disorder, lack of social support, higher level of insight, higher education level and hopelessness. Studies have investigated associations between insomnia and suicidal thinking and behavior in patients with schizophrenia. A retrospective study of 106 subjects with prodromal psychosis found that insomnia was associated with increased suicidal ideation, but not suicide attempt.

Keywords: Insomnia, Suicide, Schizophrenia

Introduction: Insomnia is a common comorbid condition in patients with schizophrenia. Accumulating evidence has suggested that sleep disturbance can be a risk factor for, or a prodromal symptom of psychosis; it can also aggravate psychotic symptoms, therefore interfering with the treatment of schizophrenia **(1).**

Symptoms related to disordered sleep, including reduced sleep time and quality of sleep, often go untreated and persist as chronic, clinically significant insomnia. Findings in polysomnography (PSG) studies such as increased sleep latency, reduced rapid eye

movement (REM) latency, and reduced spindle activity correlate with the elevated rates of sleep disturbance and sleep disorders among patients with schizophrenia **(2)**.

Notably, observed abnormalities in these polysomnographic traits have been shown to be heritable, thus further strengthening the argument for an etiological link between insomnia and schizophrenia. Clinical interest in this relationship has grown with the understanding that the presence of sleep disturbance, especially clinically significant insomnia, corresponds with reduced quality of life (QOL) and likely worse clinical outcomes for patients with schizophrenia **(3)**.

Up to 80% of patients with schizophrenia experience insomnia-related symptoms, including an inability to fall or stay asleep, or daytime somnolence. Insomnia is a disorder specifically defined by these characteristic symptoms, with acute insomnia typically lasting less than 4 weeks and chronic insomnia characterized by a longer-term pattern of disrupted sleep that lasts for over 6 months. The greater extent to which symptoms persist and affect daily function in insomnia distinguish the disorder from subthreshold or transient struggles with sleep **(4)**.

Thus, increased symptoms of sleep disturbance also correspond with a greater prevalence of clinical insomnia in patients with schizophrenia, with even conservative estimates ranging from 30 to 40% compared to a prevalence of about 10% in the general population **(3)**. A recent 2018 study estimated clinical insomnia in a population of patients with first episode psychosis at 22.6% **(5)**.

evidence suggests associations between insomnia and the severity of psychopathology in schizophrenia. We previously found insomnia was an indicator of higher psychopathology scores, as measured by Positive and Negative Syndrome Scale (PANSS) total, positive and general subscale scores ($\beta = 0.32–0.40$ for each) **(6).**

This association was replicated in the CATIE schizophrenia trial, where baseline terminal insomnia was a significant indicator of higher PANSS total, positive, and general subscale scores ($\beta = 0.11–0.14$ for each) **(6).**

A small longitudinal, pathway analysis found that insomnia was associated with hallucinations and paranoia in patients with schizophrenia **(1).** Interestingly, two studies also found associations between insomnia and greater impairments in quality of life in patients with schizophrenia **(7).**

Several neurobiological mechanisms help to explain the comorbid insomnia observed in patients with schizophrenia. Research has shown that the thalamus, a structure integral for sleep regulation, is consistently reduced bilaterally among schizophrenia patients. Thalamic

abnormalities are just one suggested neurobiological mechanism that potentially explains the intricate link between schizophrenia and insomnia **(8)**.

Other proposed mechanisms include dopamine dysregulation in schizophrenia and its simultaneous role in the sleep-wake cycle, with the dopaminergic D2 receptor, in particular, playing a specific role in REM sleep **(9).**

Overactivity of the D2 receptor, along with enhanced sensitivity of dopaminergic neurotransmission, could contribute to symptoms of insomnia. Human and animal models have shown that elevated dopamine levels in the brain disrupt sleep and circadian rhythms, whereas sleep disruption also increases dopamine release and sensitivity **(9).**

Thus, while the exact mechanism has not been clearly elucidated, dopaminergic overactivity seems to provide a viable hypothesis linking schizophrenia and insomnia. Antipsychotic agents, which block dopamine D2 receptors, often alleviate both schizophrenia and insomnia-related symptoms **(8)**.

And, in addition to antipsychotic medications, which remain the mainstay of treatment for schizophrenia , non-pharmacological interventions, which may mitigate both sleep disturbances and clinical symptoms in psychotic patients, have recently emerged. Cognitive-Behavioral Therapy for Insomnia (CBT-I) is a first-line treatment for insomnia in psychiatric population , and initial evidence suggest that CTB-I may also lead to a reduction in psychotic symptoms **(10)**.

In addition to possible neurobiological mechanisms described above, other factors, such as psychosocial stress, substance abuse, and psychotic experiences, may also contribute to the high prevalence rate of insomnia in patients with schizophrenia. Stressful life events are closely associated with the onset of chronic insomnia, and thus the high-stress environment that predisposes individuals to developing schizophrenia likely contributes to the high risk of insomnia in this patient population **(8)**.

Psychotic symptoms, such as hallucinations and delusions, can precipitate sleep disturbances and insomnia **(11)**. In addition, negative symptoms of schizophrenia, such as avolition, may lead to excessive daytime inactivity that interferes with nighttime sleep. Cognitive deficits in patients with schizophrenia can contribute to poor sleep hygiene, which further complicate the sleep pattern and quality in these patients. Furthermore, substance-induced insomnia has been well documented **(12)**; the elevated rates of substance use in patients with schizophrenia also could contribute to insomnia **(13).**

Suicide in Schizophrenia

Considerable evidence suggests that schizophrenia decreases the longevity by about 10 years . Suicide is the largest contributor to the decreased life expectancy in individuals with schizophrenia **(14)**.

Recent studies have found that the increased risk for suicidal behavior in schizophrenia is associated with the unemployment, a family history of psychiatric disorder, lack of social support, higher level of insight, higher education level and hopelessness. Patients with comorbid depressive symptoms, a family history of suicide and multiple hospitalizations are at a higher risk of suicide attempts . Comorbid substance use and more severe psychotic symptoms could also increase the risk of suicide attempts **(15)** .

In a study comparing those with and those without a history of suicide attempts among patients with either schizophrenia , better attention and executive functions were observed in the suicide group . Better insight into their illness has also been demonstrated in groups of schizophrenia patients who attempt suicide, when compared to patients that do not . They may also be more impulsive and being relatively well educated **(16**).

Also , for patients with schizophrenia , having a history of suicidal attempt is the most consistently reported risk factor for suicide . it's associated with an at least double risk of suicide compared to those without a known history of suicidal attempt

(17).

Research of first-episode patients usually has higher estimations of suicide rates than studies with lengthier follow up periods. It has been noted that during early stages of schizophrenia, limited suicidal ideation may quickly intensify to a suicide attempt. A delay in getting psychiatric treatment may substantially contribute to elevated suicide risk early in the course of schizophrenia**(14)**.

Some observations suggest that the side effects of antipsychotic medications may contribute to suicidality in individuals with schizophrenia . It has been suggested that antipsychotics-induced akathisia, akinesia, tardive dyskinesia and depressogenic effects of antipsychotic medications may increase suicide risk. For example, it has been observed that there is a significant association among akathisia and suicidality in antipsychotic use in schizophrenia **(18)**.

It has been reported that schizophrenia patients use more serious suicide methods, such as jumping in front of a train and jumping from a high place, compared to patients with other psychiatric disorders.The fact that schizophrenia patients have more lethal suicide intent

and use more serious suicide methods shows that the risk of death by suicide is higher in schizophrenia **(19)** .

A neuroimaging study using magnetic resonance imaging (MRI) investigated structural abnormalities in schizophrenia patients with suicidal behaviors and compared them to MRIs of non-suicidal patients. This study reported that gray matter density was significantly reduced in the left superior temporal lobe and left orbitofrontal cortex in suicidal patients. Another study used functional MRI to demonstrate that task-specific suppression decreased more significantly in the left medial prefrontal cortex and left posterior cingulate cortex in schizophrenia patients with suicide risk compared to healthy controls **(20).**

Another study using MRI indicated that, compared to non-attempters, attempters had significantly less gray matter volume in the bilateral inferior and superior temporal cortices, the left superior parietal, the thalamus and supramarginal regions, the right insula, and the superior, rostral middle frontal regions. The regions in which the differences were reported are part of the neural circuitries that modulate impulse control and emotion regulation. Based on previous studies, we could predict that the neuronal integrity of fronto-temporo-limbic circuits is important for suicidal behavior in schizophrenic patients **(21).**

Also hypothalamic-pituitary-adrenal axis (HPA) hyperactivity leading to glucocorticoid neurotoxicity may be the primary way through which tissue injury occurs in several parts of the brain, as observed in neuroimaging investigations of suicide attempters with schizophrenia **(14)**.

Some studies found lower 5-hydroxy acetic acid (5-HIAAA) levels in the cerebrospinal fluid (CSF) of suicidal patients in comparison to the CSF levels of non-suicidal individuals with schizophrenia . One research group found that a blunted prolactin response to a D-fenfluramine administration was associated with suicidal behavior in individuals with a history of schizophrenia. A significant link was found between single nucleotide polymorphisms ADRA2B rs1018351 and SLC6A3 rs403636 and a history of suicidal behavior in schizophrenia patients **(14)**.

Prevention of suicide focus on early detection and treatment especially the year after psychiatric admission with schizophrenia as these people are vulnerable with regard to suicidal behavior **(22)**.

Generally, the most effective and evidence based treatment for patient with firse episode psychosis is early intervention services. Several studies have examined the long term effects of early intervention on suicide rates. A long term follow up of randamised clinical trial of intensive treatment versus standard treatment showed that intensive treatment could decrease the risk of suicide up to 12 years after the first episode. In a large study, it was

shown that screening for suicidal risk in the emergency department followed by outpatient treatment could reduce suicidal behavior in the following months and years **(6).**

It's also likely that antipsychotic medications can prevent suicide. In the acute psychotic phase, antipsychotic medications can help to control the crisis. In some cases benzodiazepines can also be necessary to treat anxiety and acute agitation. In cases there's a subtle onset of psychotic symptoms, monotherapy with antipsychotic medication is indicated and its recommended to start at low dose **(17).**

Clozapine seems to have unique anti-suicidal effects. More precisely, a number of studies have investigated the potential effectiveness of clozapine in the reduction of suicidality, mainly in patients suffering from schizophrenia or schizoaffective disorder . Based on data from the International Suicide Prevention Trial (InterSePT), the Food and Drug Administration (FDA) approved clozapine as the only medication to treat suicidality manifestations in patients with schizophrenia/schizoaffective disorder **(23)**.

Another important issue in clinical practice is whether discontinuation of clozapine is associated with significantly greater risk of relapse not only of psychotic manifestations, but of suicidality symptoms in particular, when compared to continuing treatment. Notably, rates of discontinuation of antipsychotic medications in general, and of clozapine in particular are high, with the latter ranging between 20% and 60% **(23)**.

Other second-generation antipsychotics may also have anti-suicidal properties. For example, a retrospective study of the influences of atypical antipsychotic drugs on suicidal behavior in individuals with schizophrenia showed that among persons who made a suicide attempt, 16.1% took second-generation antipsychotic medications, whereas in the non-suicidal group 37% took second-generation antipsychotics. Another study has shown a fourfold rise in suicide attempts among individuals with schizophrenia who stopped taking olanzapine or risperidone **(14)**.

Comorbid depression can increase the risk of suicide behavior, and the treatment of depression and anxiety is likely to reduce risk of suicide in schizophrenia **(17).**

Insomnia and suicide in schizophrenia

Studies have investigated associations between insomnia and suicidal thinking and behavior in patients with schizophrenia. A retrospective study of 106 subjects with prodromal psychosis found that insomnia was associated with increased suicidal ideation, but not suicide attempt **(24).**

A study of 110 patients with non-affective psychosis and persecutory delusions found that insomnia, as measured by the Insomnia Severity Index (ISI), was significantly, positively correlated with the severity of suicidal ideation **(25).**

A naturalistic study in 388 outpatients with schizophrenia-spectrum disorders found a 19% prevalence of insomnia at baseline, which was associated with an almost five-fold increased risk of suicide attempt over an eight year follow-up period **(25).**

In a study of 108 patients with schizophrenia or schizoaffective disorder found that ISI scores were a significant indicator of Beck Scale for Suicide Ideation scores (β = 0.27), and patients with (versus without) severe insomnia were almost fifteen times more likely to have a history of lifetime suicide attempt **(6).**

In the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) DSM-IV schizophrenia trial,current terminal insomnia was associated with significant, 2.7-fold increased odds of current suicidal ideation, and current initial/middle insomnia was associated with a significant, 5.5-fold increased odds of suicide attempt in the past 6 months **(6).**

There is also some evidence that insomnia may also be associated with more violent suicide attempts in patients with psychiatric disorders **(26).**

Several studies have also found associations between insomnia and suicide death in schizophrenia. A small case-control study found an almost thirteen-fold increase odds of insomnia in patients with schizophrenia and suicide death compared to living males treated at the same outpatient clinic **(26).**

A meta-analysis of three case-control studies (n = 176 total subjects) found a trend-level association between sleep disturbance and suicide death in schizophrenia (OR = 1.99, 95% CI 0.96–4.12) **(27).**

Outside of schizophrenia, several studies have found that depression mediates the association between insomnia and suicidal ideation **(28)**

In schizophrenia population, insomnia was associated with suicidal ideation independent of depression in one study **(6).**, but not the other **(6).**

Therefore, patients with schizophrenia who endorse insomnia should have a rigorous assessment of both suicide risk and depressive symptoms, as even modest insomnia symptoms may be clinically meaningful in this patient population **(6).**

References:

1. Reeve, S., Sheaves, B., & Freeman, D. (2019). Sleep disorders in early psychosis: incidence, severity, and association with clinical symptoms. Schizophrenia bulletin, 45(2), 287-295.

2. D'Agostino, A., Castelnovo, A., Cavallotti, S., Casetta, C., Marcatili, M., Gambini, O., ... & Sarasso, S. (2018). Sleep endophenotypes of schizophrenia: slow waves and sleep spindles in unaffected first-degree relatives. npj Schizophrenia, 4(1), 2.
3. Xiang, Y. T., Weng, Y. Z., Leung, C. M., Tang, W. K., Lai, K. Y., & Ungvari, G. S. (2009). Prevalence and correlates of insomnia and its impact on quality of life in Chinese schizophrenia patients. Sleep, 32(1), 105-109.
4. Soehner, A. M., Kaplan, K. A., & Harvey, A. G. (2013). Insomnia comorbid to severe psychiatric illness. Sleep medicine clinics, 8(3), 361-371.
5. Subramaniam, M., Abdin, E., Shahwan, S., Satghare, P., Vaingankar, J. A., Sendren, J. R., ... & Verma, S. (2018). Prevalence, correlates and outcomes of insomnia in patients with first episode psychosis from a tertiary psychiatric institution in Singapore. General Hospital Psychiatry, 51, 15-21.
6. Miller, B. J., McCall, W. V., Xia, L., Zhang, Y., Li, W., Yao, X., & Liu, H. (2021). Insomnia, suicidal ideation, and psychopathology in Chinese patients with chronic schizophrenia. Progress in neuro-psychopharmacology and biological psychiatry, 111, 110202.
7. Batalla-Martín, D., Belzunegui-Eraso, A., Miralles Garijo, E., Martinez Martin, E., Romaní Garcia, R., Heras, J. S. M., ... & Martorell-Poveda, M. A. (2020). Insomnia in schizophrenia patients: prevalence and quality of life. International journal of environmental research and public health, 17(4), 1350.
8. Robertson, I., Cheung, A., & Fan, X. (2019). Insomnia in patients with schizophrenia: current understanding and treatment options. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 92, 235-242.
9. Ashton, A., & Jagannath, A. (2020). Disrupted sleep and circadian rhythms in schizophrenia and their interaction with dopamine signaling. Frontiers in neuroscience, 14, 636.
10. Ferrarelli, F. (2020). Sleep disturbances in schizophrenia and psychosis. Schizophrenia research, 221, 1.
11. Barrett, E. A., Aminoff, S. R., Simonsen, C., & Romm, K. L. (2020). Opening the curtains for better sleep in psychotic disorders-considerations for improving sleep treatment. Comprehensive Psychiatry, 103, 152207.
12. Khokhar, J. Y., Dwiel, L. L., Henricks, A. M., Doucette, W. T., & Green, A. I. (2018). The link between schizophrenia and substance use disorder: A unifying hypothesis. Schizophrenia research, 194, 78-85.
13. Cederlöf, E., Holm, M., Ahti, J., Lähteenvuo, M., Hietala, J., Häkkinen, K., ... & Paunio, T. (2023). Substance use and sleep problems in patients with psychotic disorders. Schizophrenia bulletin open, 4(1), sgac073.
14. Sher, L., & Kahn, R. S. (2019). Suicide in schizophrenia: an educational overview. Medicina, 55(7), 361.
15. Lu, L., Dong, M., Zhang, L., Zhu, X. M., Ungvari, G. S., Ng, C. H., ... & Xiang, Y. T. (2020). Prevalence of suicide attempts in individuals with schizophrenia: a meta-analysis of observational studies. Epidemiology and psychiatric sciences, 29, e39.
16. Pluck, G., Lekka, N. P., Sarkar, S., Lee, K. H., Bath, P. A., Sharif, O., & Woodruff, P. W. R. (2013). Clinical and neuropsychological aspects of non-fatal self-harm in schizophrenia. European Psychiatry, 28(6), 344-348.
17. Nordentoft, M., & Madsen, T. (2020). Suicide among people with psychosis in schizophrenia spectrum. Oxford Textbook of Suicidology and Suicide Prevention, 285.
18. Reutfors, J., Clapham, E., Bahmanyar, S., Brandt, L., Jönsson, E. G., Ekbom, A., ... & Ösby, U. (2016). Suicide risk and antipsychotic side effects in schizophrenia: nested case–control study. Human Psychopharmacology: Clinical and Experimental, 31(4), 341-345.
19. Aydın, M., İlhan, B. Ç., Tekdemir, R., Çokünlü, Y., Erbasan, V., & Altınbaş, K. (2019). Suicide attempts and related factors in schizophrenia patients. Saudi medical journal, 40(5), 475.

20. Zhang, L., Verwer, R. W., Zhao, J., Huitinga, I., Lucassen, P. J., & Swaab, D. F. (2021). Changes in glial gene expression in the prefrontal cortex in relation to major depressive disorder, suicide and psychotic features. Journal of affective disorders, 295, 893-903.
21. Lee, S. J., Kim, B., Oh, D., Kim, M. K., Kim, K. H., Bang, S. Y., ... & Lee, S. H. (2016). White matter alterations associated with suicide in patients with schizophrenia or schizophreniform disorder. Psychiatry Research: Neuroimaging, 248, 23-29.
22. Simon, G. E., Stewart, C., Yarborough, B. J., Lynch, F., Coleman, K. J., Beck, A., ... & Hunkeler, E. M. (2018). Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adults. JAMA psychiatry, 75(3), 254-260.
23. Masdrakis, V. G., & Baldwin, D. S. (2023). Prevention of suicide by clozapine in mental disorders: systematic review. European Neuropsychopharmacology, 69, 4-23.
24. Andriopoulos, I., Ellul, J., Skokou, M., & Beratis, S. (2011). Suicidality in the "prodromal" phase of schizophrenia. Comprehensive Psychiatry, 52(5), 479-485.
25. Freeman, D., Bold, E., Chadwick, E., Taylor, K. M., Collett, N., Diamond, R., ... & Waite, F. (2019). Suicidal ideation and behaviour in patients with persecutory delusions: Prevalence, symptom associations, and psychological correlates. Comprehensive Psychiatry, 93, 41-47.
26. Pompili, M., Lester, D., Grispini, A., Innamorati, M., Calandro, F., Iliceto, P., ... & Girardi, P. (2009). Completed suicide in schizophrenia: evidence from a case-control study. Psychiatry Research, 167(3), 251-257.
27. Hawton, K., Sutton, L., Haw, C., Sinclair, J., & Deeks, J. J. (2005). Schizophrenia and suicide: systematic review of risk factors. The British Journal of Psychiatry, 187(1), 9-20.
28. Kato, T. (2014). Insomnia symptoms, depressive symptoms, and suicide ideation in Japanese white-collar employees. International journal of behavioral medicine, 21, 506-510.