

Perception of Patients and Caregivers towards Protective and Risk Factors for Relapse in First-Episode Schizophrenia

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Abstract

Schizophrenia is a common public health problem in Thailand. Antipsychotic drugs are effective in First-Episode Schizophrenia (FES) patients. However, FES patients have a chance of relapse, which can impair mental functions, imposing a burden on family and society. Factors related to relapse are multifactorial and divergent among cultures. Identifying the right factors would help prevent the relapse. The aim of the present qualitative research study was to study protective and risk factors related to relapse in FES from perspectives of patients and caregivers. Participants were ten of FES patients who had been diagnosed with schizophrenia within two years from a tertiary psychiatric hospital of northeastern Thailand; and ten of their primary caregivers. Data were collected by audio records using a semi-structured interview schedule and in-depth interviews. Content analyses were used to determine patients and caregiver's perception of factors that influence relapse risk. Results showed that protective factors for relapse in FES were related to drug adherence (continuous use of drugs, good insight, and understanding side effects of medication), and family supportiveness (competent caregiver, literacy on schizophrenia, and positive family's attitude). Meanwhile, risk factors were drug non-adherence (uncontinuous use of drugs, lack of insight, and self-discontinuation of medication), family unsupportiveness (incompetent caregiver, illiteracy on schizophrenia, negative family's attitude, and poverty), substance abuses, psychosocial stress, and natural course of disease. To conclude, health professionals should continuously monitor all protective and risk factors in order to prevent psychotic relapse in FES.

Keywords: First-episode schizophrenia • Drug adherence • Substance abuse • Care givers

Introduction

Schizophrenia is severe psychiatric disorder listed as one of the top 20 causes of disability [1]. It is characterised by diverse psychopathology that affects not only the patient, but also the life-long caregiver and family members with lifetime prevalence of 0.7% [2,3]. The key features are manifested by positive symptoms (suspiciousness, hallucinations, delusions, impaired cognitive ability, and disorganized speech or behavior) and negative symptoms (impairments in attention and motivation, social withdrawal, reduction in spontaneous speech, and affective flattening in particular impaired motivation, and social withdrawal) [4-6]. Schizophrenia treatments include pharmacological approach and non-pharmacological approach such cognitive behavioral therapy, compliance therapy, and mindfulness therapy as an addition to medications [5]. After recovery from psychotic symptoms, First-Episode Schizophrenia (FES) patients can experience relapse of psychosis. Relapse in schizophrenia is associated with functional decline, poor treatment response and clinical outcomes, imposing a heavy burden on families and society [7]. A pooled prevalence of relapse in the first year after FES is 28% and ascends to 43% in the second year [8]. Protective and risk factors for relapse vary among different contexts of family environments, cultures, ethnicity, and countries [2]. We recently reported protective and risk factors of relapse in FES from perspective of mental health professionals in northeastern Thailand [9]. Therefore, the present study was aimed to identify protective and risk factors in patients with FES from perspectives of patients and primary caregivers.

Methods

Study design and participants

This study is a thematic exploratory study employing a qualitative generic inductive approach using Caeli's generic principles and using in-depth semi-structured interviews and focus group of ten FES patients and their primary caregivers to identify the protective and risk factors for relapse in the patients [10]. The FES patients and their primary caregivers participating in the study were purposively sampled from the outpatient department of Khon Kaen Rajanagarindra Psychiatric Hospital. All participants signed informed consent. The study was carried out between December 2019 and July 2020. We have adopted COREQ Guidelines in reporting the data [11].

Procedures

The interviews consisted of two parts—demographic data and 6 items of semi-structured interviews on problems and causes of mental health status, health literacy on schizophrenia, points of care, self-perception on competency, attitude towards psychotic symptoms, and suggestions. An experienced interviewer (J.I.) unknown to the participants conducted all individual and group semi-structured interviews. All the items have been verified for content validity and index of item-objective congruence (IOC, scores ≥ 0.75 were acceptable) [12]. Ninety-minute interviews were performed and audio-recorded in Khon Kaen Rajanagarindra Psychiatric Hospital consulting rooms; and transcribed verbatim by the interviewer. Field notes were made and discussed for data saturation.

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Ethical approval

Research procedures have been approved by the Ethical Review Committee for Human Research, Mahasarakham University (approval number 225/2019) and were carried out in accordance with the ethical principles in the Declaration of Helsinki. Pseudonyms were used to protect participant's identity. Written informed consent forms were obtained from all participants. In addition, clinical research methodology has been approved by the Thai Clinical Trials Registry (TCTR) No. TCTR20190923001.

Data analysis

Audio transcripts of the interviews were translated to English and coded using an agreed scheme by three independent coders (authors J.I., K.K. and K.T.). The transcripts sorting were performed using NVivo® 11 software package for qualitative research data (QSR International, Melbourne, Australia). Data

coding and categorization were performed and highlighted into themes. The coded categories were further classified to derive a particular theme from each group using concept maps. Most representative quotations from the patients were used to support the themes. After processing data, the transcripts were given back to the participants for authentication.

Results

Demographic data of participants

Ten FES patients (seven males and three females) with mean age of 31.5 ± 12.9 years old and average length of mental illness of 9.5 ± 3.9 months and ten primary caregivers (five males and five females) with mean age of 53.4 ± 8.5 years old and average length of caregiving of 8.6 ± 4.2 months. All details are shown in Tables 1 and 2.

Table 1. Characteristics of first-episode schizophrenia patients.

Initial	Gender	Age	Marital status	Education	Job	Income (baht)	Length of illness (month)	Drug abuse
Pt1	Female	19	Single	High school	Student	0	12	Smoking
Pt2	Female	41	Single	High school	Employee	6,000	3	No
Pt3	Male	23	Single	High school	Employee	10,000	9	Amphetamine
Pt4	Male	28	Single	High school	Seller	5,000	11	No
Pt5	Female	51	Single	Primary school	Employee	6,000	12	No
Pt6	Male	25	Single	High school	Unemployed	0	13	No
Pt7	Male	32	Single	Primary school	Seller	20,000	12	Amphetamine
Pt8	Male	17	Single	High school	Unemployed	0	2	No
Pt9	Male	54	Single	Primary school	Employee	6,000	12	Alcohol
Pt10	Male	25	Single	High school	Unemployed	0	9	Amphetamine

Table 2. Characteristics of primary caregivers.

Initial	Gender	Age	Marital status	Education	Job	Income (baht)	Length of caregiving (month)	Relationship with patient
Cg1	Male	52	Married	High school	Seller	15,000	12	Father
Cg 2	Male	70	Married	Primary school	Farmer	10,000	3	Father
Cg 3	Female	48	Separate	Primary school	Employee	9,000	9	Mother
Cg 4	Female	49	Divorce	Primary school	Seller	5,000	11	Mother
Cg 5	Female	63	Single	Primary school	Retired	6,000	12	Aunt
Cg 6	Female	51	Married	Primary school	Employee	9,000	13	Father
Cg 7	Male	50	Married	Primary school	Seller	20,000	12	Father
Cg 8	Male	48	Single	Primary school	Employee	6,000	2	Father
Cg 9	Male	61	Married	Primary school	Employee	5,000	3	Husband
Cg10	Female	42	Divorce	High school	Employee	10,000	9	Mother

Protective and risk factors

After the data were analyzed with the software, protective and risk factors were categorized into five main themes: drug adherence, family factors, substance abuses, psychological stress, and natural course of disease as summarized in Table 3.

Table 3. Themes and subthemes constructed from the semi-structured interviews of the patients and primary caregivers.

Protective Factors	Risk Factors
1. Drug adherence	1. Drug non-adherence
1.1) Continuous use of drugs	1.1) Uncontinuous use of drugs
1.2) Understanding side effects of medication	1.2) Lack of insight
1.3) Good insight	1.3) Self-discontinuation of medication
2. Supportive family	2. Unsupportive family
2.1) Competent caregiver	2.1) Incompetent caregiver
2.2) Literacy on schizophrenia	2.2) Illiteracy on schizophrenia
2.3) Positive family's attitude	2.3) Negative family's attitude
	2.4) Poverty
	3. Substance abuses
	4. Psychosocial stress
	4.1) Stressful circumstances
	4.2) Loss events
	4.3) High expressed emotion
	5. Natural course of disease

Theme 1: Drug adherence vs non-adherence

The key informants perceived the reasons for cooperation on medication adherence behaviors from the following 3 subthemes: continuous vs uncontinuous use of drugs, understanding side effects of medication vs self-discontinuation of medication, and good insight vs lack of insight. Details are enumerated as follows.

Subtheme 1.1-Continuous vs uncontinuous use of drugs: Patients took antipsychotic drugs until they felt better. They thought that they were fully recovered and hence skipped or not continuously taking drugs. Other reasons were unawareness of importance of the drugs, forgetfulness, and fear of side effects, which can be explained in the following interviews:

Patient 1: "No... I won't take any medication. It doesn't work for me."

Patient 1's father: "The problem was that she refused to take medicine. She had meal but refused to take medicine that doctor gave him."

Patient 6: "Ah... this drug... I won't take it... my symptom won't get any better. It doesn't help."

Patient 4: "I used to forget taking drug for few days, but it's ok now. My mom reminds me."

Patient 5's sister: "Taking drug?... It's hard to do that... If she cooperated in taking it, it would be easier."

Patient 5's sister: "It's hard to remember how long that my sister didn't take drug. And I can't bring her to hospital, because I have responsibility to care my grandmother."

Subtheme 1.2-Understanding side effects of medication vs Self-discontinuation of medication: Patients taking the drug and having side effects from the drug occur, resulting that patient being unwell, unable to perform daily activities or work, impair the reputation, therefore patients had to reduce dose of their medication by himself. They did not come to see the doctor, or stopped taking drug by themselves, which can be explained in the

following interviews:

Patient 10: "Taking drug is difficult for me. I felt like having hard respiration, dry saliva, sticky mouth and sticky throat, moreover, I had got debility, and hard to walk in that time, but now I feel better."

Patient 2: "When I got up, I felt dizzy."

Patient 8: "That made me feel suffering (head down and low tone). I had got dry throat and dizzy for 10 seconds"

Patient 10's mother: "He always says he is tired in no time."

Subtheme 1.3-Good insight vs lack of insight: Patients perceive psychotic symptoms as neither abnormal nor mentally ill. So, no medication or healthcare is required, which can be explained in the following statements:

Patient 6: "I don't know the cause of symptoms. I only come to the hospital for an appointment."

Patient 1's father: "Um... she didn't take drugs... she said that she was fine."

On the other hand, patients who well cooperated with treatment had a positive effect on long-term health. In other words, they would be calm or the symptoms of schizophrenia disappeared; and they realized importance of continuous treatments. They would be able to self-arrange their own medication and picked up the medication from pharmacists to continue taking, details were shown as follows.

Patient 9: "I always take medication by myself... and I come to hospital for continuing taking."

Patient 4: "Now, I am better... so my mom let me come here by myself." (follow-up visits at the hospital)

Patient 2: "I can be able to arrange my own medication."

Patient 4: "I can do it myself. I can do everything without helps from others like taking a shower, dressing up, working, eating, and going to bed."

Patient 10: "Now, I am fine, I take medication by myself."

Patient 7: "I didn't feel sleepy, I only take it at night, then sleep."

Theme 2: Supportive vs unsupportive family

The patients and primary caregivers perceived that relapse was associated with supportiveness of caregivers or family members. This can be divided into 4 subthemes: competent vs incompetent caregiver, literacy vs illiteracy on schizophrenia, positive vs negative family's attitude, and poverty as shown below.

Subtheme 2.1-Competent vs incompetent caregiver: Caregivers were not competent enough to control and monitor patient's cooperation in the following issues: medication adherence, follow-up appointment, substance abuse avoidance, and continuous encouragement as narrated here.

Patient 10's mother: "I find that my son always refuses to take medication. He said it caused him headache and dizziness. So, I didn't want to force him take medication."

Patient 5's sister: "I couldn't remember an appointment with the doctor. I has passed for a month, but I didn't even have enough time caring for my sister."

Patient 7: "My parents were also largely involved in my mental health, they helped me talk to the doctor and reminded me of taking medication on time."

Patient 5's sister: "Taking medication, she would do it, if she didn't walk away somewhere."

Patient 10's mother: "I told him to go to work, but he said he was really tired. So, I didn't want to force him."

Patient 4: "I used to forget taking medication for few days, but then my mom reminded me."

Patient 8's father: "My son always uses smartphone. In the past, he helped me to do housework. But for now, if I say anything he doesn't like, he will become

irritated and hurt himself. I want you to treat this problem.”

Patient 9: “Even if I told him, he didn't follow it. I couldn't control him to do anything. Before the new year, I saw that he was secretly drinking alcohol, but he was still taking medicine.”

Subtheme 2.2-Literacy vs illiteracy on schizophrenia: Relatives and caregivers lacked a proper understanding of the causes, symptoms, care, treatment and prevention of relapses, which can be explained in the following interviews:

Patient 10's mother: “He always feels alone. He doesn't go outside with his friends and doesn't talk to anybody even family member. He has been like this for 2-3 month after his father died. I think he feels depressed.”

Patient 2's father: “I don't know how to cure my son's disease because I've never encountered this kind of disease before. When I told him to take medicine, he always got irritated. Then I decided to take him to the doctor.”

Patient 10's mother: “I don't know if this disease is related to laziness or not. I saw that after he took those pills, he slept all day and did nothing.” On the other hand, if the caregivers have a good understanding of schizophrenia and are able to provide good care, they can help support the patient.

On the other hand, if the caregivers were perceptive of schizophrenia and were able to provide good care, they could help support the patient. This is depicted in the following interviews.

Patient 10: “My mom is my caregiver; she is responsible for cooking for me. She also warned me to avoid alcohol.”

Patient 7: “My parents got involved a lot in my mental health, they helped me talk to the doctor and helped me to take my medication on time.”

Patient 9: “I had to control my brother. I saw a person who was schizophrenia and their didn't care themselves, their hair and nails weren't cut, that was look bad.”

Patient 1's father: “When looking into schizophrenia, it has been described that schizophrenia consists of isolation and hearing loss, for which these symptoms should be treated by caregivers.”

Subtheme 2.3-Positive vs negative family's attitude: In the early stages, both patients and their caregivers had negative feelings, such as embarrassment, reluctance to admit that they were mentally ill and deny their illness, patients would not cooperate in treatment or caregiver will not take patient for treatment, which can be explained in the following statement:

Patient 2: “Yes, I'm embarrassed. I've never though that I would have got this disease.”

Patient 10: “Yes...embarrassing.”

Patient 6: “Ah... these drugs... I can't take them.”

Patient 1: “No... I will not take any drugs. These won't help me with anything.”

Patient 2's father: “Being (mentally ill) make us feel embarrassed.”

Patient 5's sister: “It's embarrassing, she will ask for money with everyone.”

Patient 1's father: “Um... she didn't take drugs... she said that she was fine.”

The positive attitude was to be acknowledge illness. Caregivers and relatives will help bring patients to treatment while providing care, support, and encouragement to each other, which can be explained in the following interviews:

Patient 1's father: “I always tell my daughter not to think too much, everything can start over so don't overthink it, we should focus on curing this disease first.”

Patient 1's father: I want to take the best care of my daughter, treat it with conventional medicine and also rely on faith therapy, to heal and sustain her mind as much as possible.

Subtheme 2.4-Poverty: Patients and their caregivers were poor in rural areas, lacking in facilities and having difficulty receiving continued treatment, which

can be explained in the following interviews:

Patient 8's father: “My son has got this disease. I have to quit my job. My wife has to work alone, only me that has to take care of him. We rent a house and have no any assets. Another kid is also at school. I come here by bus back and forth like this. Once I was hired and he was with me. You know, he sneaked away and it was so difficult to find him back.”

Patient 2: “I used to work in factory, but now I'm unemployed.”

Patient 10: “No income. I don't even have enough money to buy new clothes, now I'm just using the old stuff.”

Patient 1's father: “My income is not that much, about 7,000 – 8,000 baht per month, just enough for living.”

Patient 5's sister: “In the past, she worked in construction and earned 300 baht a day (minimum wage in Thailand); but now he is ill, it's difficult to work like before.”

Patient 5's sister: “The mayor sometimes gives us food. Grandma receive money and elderly welfare card from government.”

Theme 3: Substance abuse

The participants addressed narcotic drugs such as methamphetamines (meth pills and crystal meth), alcohols, and cigarettes as problems in caring schizophrenia patients. Besides, psychostimulant agents (energy drinks, coffee, and diet pills) were also risk factors as mentioned below.

Patient 7: “I used to drink alcohol; and smoke cigarettes and methamphetamines after meal. That made me feel crazy, but now I give up.”

Patient 7: “If I go back to use it, I'm sure I'll be going crazy again.”

Patient 10: “Yes, I occasionally used narcotic drug, but it wasn't too much, only few pills and I don't use it anymore.”

Patient 9: “Alcohol... in the past, I used to occasionally drink and used cigarettes for 3 times a day.”

Patient 8: “I drink two cans of coffee a day.”

Patient 6 “I only drink when I sometimes get depressed. I drink 4-5 bottles of alcohol, hoping to forget bad time in my life.”

Patient 10's mother: “Methamphetamines...I thought that my son would not get involved with these kinds of things, but I was wrong. He also drank a lot and he's got hallucination.”

Patient 1's father: “The reason is...there must be something in his brain too. It had to be about taking a white pill drug (methamphetamine) that destroyed the brain.”

Patient 1: “Collagen (nickname of weight loss diet pill for some teenagers). I just take totally 60 capsules, one capsule a day before bedtime, you will see results.”

Theme 4: Psychosocial stress

The interviewees ascribed relapse in FES patients to different forms of psychosocial stress including stressful circumstances, loss events, and high expressed emotion as addressed below.

Subtheme 4.1-Stressful circumstances: Patients were exposed to stressful conditions and lacked of skills in coping with stress or inappropriately expressing their distress. This eventually made them unable to manage their stressful circumstances as shown in the following messages.

Patient 2: “When I was exposed to stressful conditions... My mind was abnormal.”

Patient 8: “When I had a depression and didn't take it out, I was always stressed.”

Subtheme 4.2-Loss events: Losing patient's important persons or disappointment from love or work could make psychotic symptoms, which can be explained in the following interviews:

Patient 10's mother: "He is always alone; he didn't go outside with his friends and didn't talk with everyone whether family member or someone. He had been like this for 2-3 month after his father died. I think he is depressed."

Patient 6: "In that time, I could cope with my depressed, until I lost my work, it made me feel, unhappy, sad and finally I was depressed"

Patient 2's father: "I heard that they would promote him as a manager. Anyway, for some reasons, he didn't get promoted. This might be a cause of his psychotic symptoms"

Patient 6: "I experienced failure in both work and love."

Subtheme 4.3-High expressed emotion: High expressed emotion is a condition within a family where strong emotions are expressed and conflicts arise between family members as illustrated below.

Patient 7: "Verbal fight with my parents and girlfriend also pushed me to use narcotic drugs."

Theme 5: Natural course of disease

Natural course of schizophrenia is uncontrollable. Despite comprehensive treatment plan and satisfactory cooperation of the patients and caregivers, relapse still develops as addressed below.

Mother 4: "I always take medicines, but it still come back. The doctor said it was nature of the disease to come back anytime."

Discussion

As relapse of FES is dependent on various factors, an overreaching objective of this present study was to determine protective and risk factors associated with relapse in FES from perspectives of the outpatients of the Khon Kaen Rajanagarindra Psychiatric Hospital and their primary caregivers. Protective factors were drug adherence and family supportiveness; while risk factors were drug non-adherence (uncontinuous use of drugs, lack of insight, and self-discontinuation of medication), family unsupportiveness (incompetent caregiver, illiteracy on schizophrenia, negative family's attitude, and poverty), substance abuses, psychosocial stress, and natural course of disease.

Adherence to medication is pivotal to successful treatments of schizophrenia. Approximately 70% of schizophrenia patients well responsive to pharmacological treatments [13]. Drug non-adherence can result in rehospitalization, poor quality of life, illness exacerbation, reduction of effectiveness of subsequent treatments, relapse of psychotic symptoms, and suicide probability [14-16]. Most clinical practice guidelines suggest at least 1-2 years of antipsychotic treatments after symptom remission of the FES [3,17]. However, according to the vulnerability/stress model of schizophrenic relapse, many patients discontinue taking medication due to cognitive functional impairment and side effects of the antipsychotic drugs [18]. As previously mentioned, the patients in Thailand have limitation of access to the atypical antipsychotics, which have relatively less side effects [9]. In addition, drug non-adherence is also interrelated to poor insight of patients and family about their illness and treatments [14].

In Thailand, after the first psychotic event, patients are admitted to the hospital for a short period (7-14 days in case of the Khon Kaen Rajanagarindra Psychiatric Hospital). When symptoms subside, the patients are directed to rehabilitate at home. This transitional period is called deinstitutionalization – the patients are subject to behavioral adaptation to community environment [19]. At this point, family members are best to assist patients in aspects continuous medication, social activity participation, and self-caring [20]. Evans and Moltzen defined six important domains of competent caregiver behaviors and styles – acceptance, creating a positive atmosphere, expectations of change, responsiveness, normalization, and educativeness [21]. Meanwhile, Mamnuah suggested that the family had four roles in preventing recurrence – acceptance, assistance, hope, and communication [22]. Therefore, it can be compiled that one of desirable characteristics of a good caregiver is being educative with positive attitude. The caregiver burden in northeastern Thailand seems to be greater than other developed countries that have more psychiatric beds such as Germany [23]. While keeping their mindsets positive attitude towards

mental illness management, the caregivers have to strive for economic income. Therefore, it is difficult for them to maintain good quality of care while living from hand to mouth. As a consequence, the patients are not well nurtured and have a chance to divagate and use narcotic substances.

Drug abuse is on top of the list of psychotic symptom aggravators. According to a longitudinal study by Wade and colleagues, it can double the rate of relapse in FES [24]. In addition to known effects of tobacco, methamphetamine, and alcohols, the patients in our study were not aware of using diet pills, coffee, and energy drinks. Three out of four schizophrenia patients use at least one of these psychoactive substances, which are also have high comorbidity with schizophrenia [25,26]. The patients use these substances partially due to psychological stress, which share the same neuronal pathway, a hypothalamic-pituitary-adrenal (HPA) axis [27].

Stress is defined as any unpredictable or uncontrollable event that exceeds the regulatory capacity of an organism [28]. Psychosocial stress caused by any stressful events activates periventricular nucleus of the hypothalamus, increasing release of corticotropin releasing factor and arginine vasopressin, triggering release of adrenocorticotrophic hormone from the anterior pituitary, and stimulating a stress hormone, glucocorticoid secretion from adrenal cortex [29]. Narcotic substances exert similar effects on HPA axis as stressors, explaining why the patients use them when they feel stressed [30]. Of note, individuals living in family environments typified by high levels of hostility, criticism and emotional over involvement (i.e. high-expressed emotion) are significantly more at risk for relapse than persons who live with families who do not display these behaviors [31]. The more the emotion expressed in family members, the more frequent relapses were seen among the patients with schizophrenia [32]. Personal burdens for a patient's behavior are more likely to result in critical and hostile responses, which place the patient at higher risk of relapse [21]. However, some patients still manifest relapse regardless of their well cooperation in medication adherence and treatment process [33]. This is partially due to spontaneous dopamine hyperactivity [34]. Brain pathology is another potential cause of relapse in the FES.

Conclusion

Schizophrenia patients and their primary caregivers reflected that medication adherence and family supportiveness were protective factors for relapse prevention in FES. Meanwhile, medication non-adherence, family unsupportiveness, substance abuses, and psychological stress were risk factors for relapse prevention in FES. Therefore, these factors should be taken into account of strategic planning for FES treatments.

Competing Interests

No competing interests were disclosed.

References

1. "Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study." *Lancet* (2017): 1259.
2. Gurak, Kayla and Amy Weisman De Mamani. "Risk and Protective Factors, Perceptions of Family Environment, Ethnicity, and Schizophrenia Symptoms." *J Nerv Ment Dis* 204 (2016): 570.
3. Keepers, George A, Laura J Fochtmann, Joan M Anzia and Sheldon Benjamin, et al. "The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia." *Am J Psychiatry* 177 (2020): 868-872.
4. Jablensky, Assen. "The Diagnostic Concept of Schizophrenia: Its History, Evolution, and Future Prospects." *Dialogues Clinical neuroscience* 12 (2010): 271.

5. Patel, Krishna R, Jessica Cherian, Kunj Gohil and Dylan Atkinson. "Schizophrenia: Overview and Treatment Options." *Pharmacy Therapeutics* 39 (2014): 638.
6. Owen, MJ, A Sawa and PB Mortensen. "Schizophrenia". *Lancet* 388 (2016): 86-97.
7. Alphas, Larry, Henry A Nasrallah, Cynthia A Bossie and Dong-Jing Fu, et al. "Factors Associated with Relapse in Schizophrenia Despite Adherence to Long-Acting Injectable Antipsychotic Therapy." *Int Clin psychopharmacol* 31 (2016): 202-209.
8. Alvarez-Jimenez, Mario, A Priede, SE Hetrick and Sarah Bendall, et al. "Risk Factors for Relapse Following Treatment for First Episode Psychosis: A Systematic Review and Meta-Analysis of Longitudinal Studies." *Schizophr Res* 139 (2012): 116-128.
9. Intharit, Jarunee, Khanogwan Kittiwattanagul, Wisit Chaveepojnkamjorn and Kukiat Tudpor. "Risk and Protective Factors of Relapse in Patients with First-Episode Schizophrenia from Perspectives of Health Professionals: A Qualitative Study in North Eastern Thailand." *Research* 10 (2021): 499.
10. Caelli, Kate, Lynne Ray and Judy Mill. "Clear as Mud": Toward Greater Clarity in Generic Qualitative Research." *Int J Qualitative Methods* 2 (2003): 1-13.
11. Tong, Allison, Peter Sainsbury and Jonathan Craig. "Consolidated Criteria for Reporting Qualitative Research (COREQ): A 32-Item Checklist for Interviews and Focus Groups." *Int J Qual Health Care* 19 (2007): 349-357.
12. Turner, Ronna C, and Laurie Carlson. "Indexes of Item-Objective Congruence for Multidimensional Items." *Int J Testing* 3 (2003): 163-171.
13. Zipursky, Robert B. "Why are the Outcomes in Patients with Schizophrenia so Poor?." *J Clin Psychiatry* 75 (2014): 1-2.
14. Semahegn, Agumasie, Kwasi Torpey, Adom Manu and Nega Assefa, et al. "Psychotropic Medication Non-Adherence and its Associated Factors Among Patients with Major Psychiatric Disorders: A Systematic Review and Meta-analysis." *Syst Rev* 9 (2020): 1-18.
15. Farooq, Saeed and Farooq Naeem. "Tackling Nonadherence in Psychiatric Disorders: Current Opinion." *Neuropsychiatr Dis Treat* 10 (2014): 1069.
16. Lacro, Jonathan P, Laura B Dunn, Christian R Dolder and Dilip V Jeste. "Prevalence of and Risk Factors for Medication Nonadherence in Patients with Schizophrenia: A Comprehensive Review of Recent Literature." *J Clin Psychiatry* 63 (2002): 892-909.
17. Correll, Christoph U, Jose M Rubio and John M Kane. "What is the Risk-Benefit Ratio of Long-Term Antipsychotic Treatment in People with Schizophrenia?." *World Psychiatry* 17 (2018): 149-160.
18. Nuechterlein, Keith H, Michael E. Dawson, Joseph Ventura and Michael Gitlin, et al. "The Vulnerability/Stress Model of Schizophrenic Relapse: A Longitudinal Study." *Acta Psychiatr Scand Suppl* 89 (1994): 58-64.
19. Kunitoh, Namino. "From Hospital to the Community: The Influence of Deinstitutionalization on Discharged Long-Stay Psychiatric Patients." *Psychiatry Clin Neurosci* 67 (2013): 384-396.
20. Loukissa, Dimitra A. "Family Burden in Chronic Mental Illness: A Review of Research Studies." *J Adv Nurs* 21 (1995): 248-255.
21. Evans, Ian M and Natasha L Moltzen. "Defining Effective Community Support for Long-Term Psychiatric Patients According to Behavioural Principles." *Aust N Z J Psychiatry* 34 (2000): 637-644.
22. Mamnuah M. "The Role of the Family in Preventing Relapse of Schizophrenia Patient." *J Med Sci* 9 (2021): 44-9.
23. Roick, Christiane, Dirk Heider, Paul E Bebbington and Matthias C Angermeyer, et al. "Burden on Caregivers of People with Schizophrenia: Comparison Between Germany and Britain." *Br J Psychiatry* 190 (2007): 333-338.
24. Wade, Darryl, Susan Harrigan, Jaymi Edwards and Philip M Burgess, et al. "Substance Misuse in First-Episode Psychosis: 15-month Prospective Follow-up Study." *British J Psychiatry* 189 (2006): 229-234.
25. Mauri, MC, Lucia S Volonteri, Ilaria F De Gaspari and Alessandro Colasanti, et al. "Substance Abuse in First-Episode Schizophrenic Patients: A Retrospective Study." *Clin Pract Epidemiol Ment Health* 2 (2006): 1-8.
26. Banyal, Navdeep, Debajyoti Bhattacharyya and Prateek Yadav. "Study to Determine the Prevalence of Substance Use and Factors Associated with it, in First-Episode of Psychosis." *Ind Psychiatry J* 27 (2018): 264.
27. Lijffijt, Marijn, Kesong Hu and Alan C Swann. "Stress Modulates Illness-Course of Substance use Disorders: A Translational Review." *Front Psychiatry* 5 (2014): 83.
28. Koolhaas, Jaap M, Alessandro Bartolomucci, Bauke Buwalda and Seitse F de Boer, et al. "Stress Revisited: A Critical Evaluation of the Stress Concept." *Neurosci Biobehav Rev* 35 (2011): 1291-1301.
29. Dedovic, Katarina, Annie Duchesne, Julie Andrews and Veronika Engert, et al. "The Brain and the Stress Axis: The Neural Correlates of Cortisol Regulation in Response to Stress." *Neuroimage* 47 (2009): 864-871.
30. Armario, Antonio. "Activation of the Hypothalamic-Pituitary-Adrenal Axis by Addictive Drugs: Different Pathways, Common Outcome." *Trends Pharmacol Sci* 31 (2010): 318-35.
31. Kavanagh, David J "Recent Developments in Expressed Emotion and Schizophrenia." *Br J Psychiatry* 160 (1992): 601-620.
32. Rashidpour, Parvane, SM Ardekani, Hossein Abouzari and Fatemeh Hosseini, et al. "The Effect of Family-Expressed Emotion on Schizophrenia Relapse Rate." *J Critical Rev* 6 (2019): 252-258.
33. Chen, Eric YH, Christy LM Hui, May ML Lam and Cindy PY Chiu et al. "Maintenance Treatment with Quetiapine Versus Discontinuation After One Year of Treatment in Patients with Remitted First Episode Psychosis: Randomised Controlled Trial." *Bmj* 341 (2010): 25.
34. Dorph-Petersen, Karl-Anton and David A Lewis. "Postmortem Structural Studies of the Thalamus in Schizophrenia." *Schizophr Res* 180 (2017): 28-35.

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