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Literature Review

Impact of Duration of Untreated Psychosis on Cognitive Function in Schizophrenia

Rina Krismiati Gani [1,2], Erikavitri Yulianti [2,3], Ifa Tunisya[4]

[1]Dr. Slamet Martodirdjo General Hospital, Pamekasan, Indonesia
[2]Department of Psychiatry, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Dr. Soetomo General Hospital, Surabaya, Indonesia
[4]Department of Psychiatry, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia

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*) Corresponding author:
E-mail: rikahus@yahoo.co.id

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Abstract

Background: Schizophrenia is a chronic and serious clinical syndrome with very aggravating psychopathology involving perception, cognition, emotion, and behaviour. Currently, cognitive dysfunction is seen as a core disorder of schizophrenia. Duration of Untreated Psychosis (DUP) refers to the period from the onset of psychotic symptoms to the first adequate administration of antipsychotics.
Aims: This review aims to analyse the impact of DUP on cognitive function in schizophrenia.
Methods: PubMed and Google Scholar were searched using the following keyword: (cognitive function) and (neurodevelopmental OR neurotoxicity hypothesis) and (duration of untreated psychosis or DUP) and (schizophrenia or psychosis or psychotic) using the journal publication filter for the 2014-2020 issue. We also used textbooks published in the last 10 years and were related to writing themes.
Review: There are two different opinions about the impact of DUP on the cognitive function of schizophrenic patients: (1) the neurodevelopmental hypothesis says there is no impact of the length of DUP on the cognitive function of schizophrenic patients; (2) the neurotoxicity hypothesis says the length of the DUP will impact the patient's cognitive function. Despite differences of opinion about the impact of DUP on cognitive function in schizophrenia, early intervention in schizophrenic patients is important because DUP is associated with worse general disease symptoms, lower likelihood of remission, more severe positive and negative symptoms, and worse social functioning and overall outcomes.
Summary: There are differences of opinion about the impact of DUP on cognitive function in schizophrenic patients.

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INTRODUCTION

Schizophrenia is a chronic and serious clinical syndrome with very aggravating psychopathology involving perception, cognition, emotion, and behaviour. Cognitive impairment in schizophrenic patients has a significant impact on the functional degree of the individual. Cognitive deficits in schizophrenia not only occur in chronic patients, but also occur in the first episode. Currently, cognitive dysfunction is seen as a core disorder of schizophrenia [1], [2]. Not all schizophrenic patients experience cognitive impairment. Some still have cognitive level scores that are normal or above normal with a prevalence of 15-45%. However, 64% of them still had abnormal scores in one cognitive domain, when compared to the healthy control group. The majority of sufferers did have a cognitive level below the healthy control group, at least one standard deviation. [3].

Duration of Untreated Psychosis (DUP) refers to the period from the onset of psychotic symptoms to the first adequate administration of antipsychotics. The initial psychotic phase will follow the manifestations of the first episode of psychotics which have an important impact on the patient's long-term journey. Need to intervene as early as possible and stop delays in treatment. Several studies have revealed different results regarding the relationship of DUP with cognitive function in schizophrenic patients. Some indicate a positive relationship and some are negative. These differences also included worse manifestations of positive and negative symptoms, lower neurocognitive abilities, poor premorbid function, and lower levels of social functioning. [4].

AIMS

Since the onset of psychotic symptoms in schizophrenic patients, various processes occur in the patient's brain. It is necessary to study what processes occur in the patient's brain during the DUP considering that DUP is a prognostic factor that can be modified to produce better outcomes in schizophrenic patients. There are two theories that underlie the occurrence of cognitive deficits in schizophrenia patients, namely the neurodevelopmental hypothesis and the neurotoxicity hypothesis [1], [2]. This review aims to analyse the impact of DUP on cognitive function in schizophrenia based on these two theories.

METHODS

PubMed and Google Scholar were searched using the following keyword: (cognitive function) AND (neurodevelopmental OR neurotoxicity hypothesis) AND (duration of untreated psychosis OR dup) AND (schizophrenia OR psychosis OR psychotic) using the journal publication filter for the 2014-2020 issue in any research design. We also used textbooks published in the last 10 years and were related to writing themes. Our searches are primarily on neurodevelopmental theory and neurotoxicity theory related to cognitive dysfunction in schizophrenia. However, journals that describe the pathophysiology of schizophrenia and the development of cognitive function are also included to clarify the theory that explains the relationship of DUP with cognitive outcomes in schizophrenic patients.

REVIEW

According to Stahl (2013) schizophrenia is a disorder with symptoms that appear within 6 months which include at least delusional symptoms, hallucinations, speech processing disorders, behavioural disorders, and negative symptoms [5]. DSM 5 (2013) uses the term of spectrum of schizophrenia and other psychotic disorders including schizophrenia, other psychotic disorders, and schizotypal disorders are used which are defined as disorders in one or more of the following five domains: delusions, hallucinations, disorganization of thought processes (speech), disorganization of motor behaviour or abnormal (including catatonia), and negative symptoms [6]. The prevalence of schizophrenia is estimated to be around 1%, meaning that 1 person in 100 people will experience schizophrenia during his lifetime [7]. Riskesdas 2018 data shows the prevalence of severe mental disorders in Indonesia, such as schizophrenia, reaching around 7 per 1,000 population, increase four times from the previous one, 1.7 per 1,000 population in 2013 [8].

Cognitive is a process in which all sensory input (tactile, visual and auditory) will be changed, processed, stored and then used for perfect interneuron relationships so that individuals are able to reason about these sensory inputs [9]. Cognition is an important function of the brain, which is an amalgamation of a mental process in order to gain knowledge and care for the surrounding environment so that it allows making appropriate decisions. Cognitive includes attention, memory, language, praxis orientation, executive functioning,

assessment, and problem-solving. Cognition affects problem-solving skills, decision making and creativity [10]. Therefore, impaired cognitive function can have an impact on personal, work, and social functions [7]. Cognitive function is influenced by age [11], intelligence quotient (IQ) [12], [13], neurotransmitters including dopamine, serotonin, norepinephrine [14], glutamate [15], GABA [16], acetylcholine [17], and genetics [18]. In schizophrenia, there are disorders of neurotransmitters that can interfere with cognitive function in humans.

Schizophrenia is usually characterized as a disorder with generalized neurocognitive dysfunction covering specific domains that are more affected than others. A new hypothesis is proposed by Luck et al (2019) which explains aspects of cognitive impairment in schizophrenia, namely the hyper-focus hypothesis. Schizophrenic patients focus their processing resources intensely even though they are very narrow. This hyper-focusing causes disruption in the distribution of attention between multiple places, causes attention to be seized by irrelevant inputs abnormally that share characteristics with active representation, and reduces the number of representations that can be preserved simultaneously in working memory[19].

The disturbances that occur are quite extensive, ranging from basic perception and motor speed to complex memory, attention and executive functions. Neurocognitive deficits are related to the functional outcome of schizophrenia patients, namely real-world functioning, quality of life, mental rehabilitation success, and functional capacity that assesses social skills [20]. This is in line with what was conveyed by Kar and Jain, namely that schizophrenic cognitive impairment causes dysfunction in the real world and significant disturbances in the quality of life. Schizophrenia causes disruption of the prefrontal cortex function through several mechanisms, including metabolic disorders, decreased perfusion, and impaired synaptic pruning. One of the functions of the prefrontal cortex is to regulate high cognitive functions, such as planning, organizing, and determining the purpose of activities. Cognitive deficits persist even during the remission phase. In Kar and Jain's opinion, the major cognitive domains affected in schizophrenia include attention and alertness; executive function; learning and memory; working memory; problem-solving; information processing and processing speed; and social cognition [10].

Until now, there is no standard definition of duration of untreated psychosis (DUP). Some authors say that DUP starts from the first appearance of psychotic symptoms, although it is brief. Another opinion says that DUP starts when psychotic symptoms last for a certain time or the degree of severity is at least in the moderate category based on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS). There is also a difference opinion about the final determination of DUP. Some argue that the end of DUP will be when antipsychotic therapy begins. However, another opinion says the end of DUP is when the patient begins to be hospitalized and gets treatment with a certain dose and duration. [1]. The most commonly used definition for DUP is the duration or period from the first onset of psychotic symptoms to initial adequate antipsychotic therapy as seen in figure 1. DUP is a variable prognostic factor [1], [4], [21].

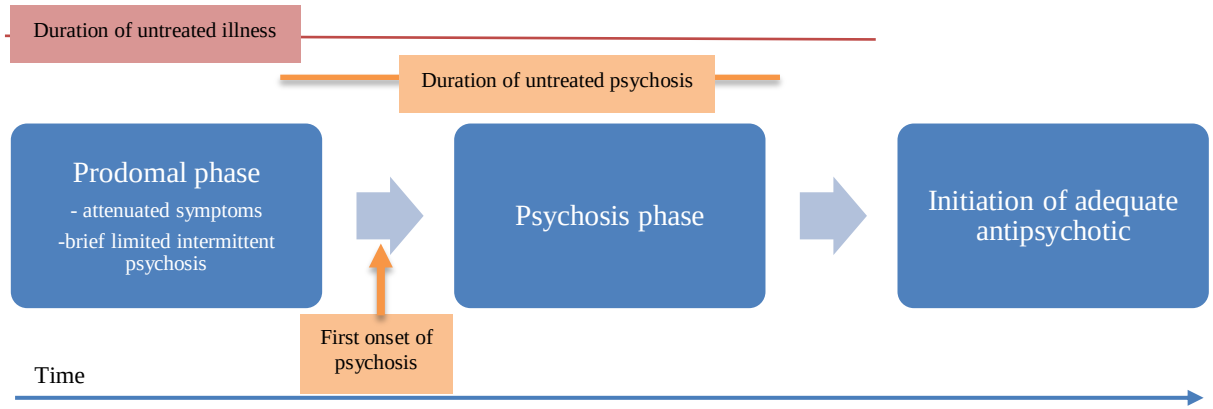

Figure 1. Measurement of duration of untreated psychosis (DUP)

The longer the patient is not treated, the longer the DUP will be. Some of the factors that cause DUP to be longer include low cognitive function, causing patients not to seek treatment immediately; low perceptiveness, for example there is denial of the disease which results in patients delaying seeking treatment; negative symptoms, especially those that cause delays

in seeking treatment, such as lack of motivation and social withdrawal; minimal positive symptoms, resulting in people around the patient not alert so it is too late to seek treatment; the onset of schizophrenia, psychotic symptoms in patients with acute-onset develop rapidly so that families find it easier to recognize and seek treatment immediately, whereas in insidious-onset symptoms that appear gradually make families realize too late so it is too late to seek treatment; culture and religion, sometimes patients with psychotic symptoms are considered possessed or exposed to witchcraft because of cultural and religious influences, so they seek treatment from healer or shaman, not medical personnel; and substance abuse [21]–[23]. From several studies, there are differences regarding the impact of DUP on cognitive function in schizophrenic patients. Some indicate a positive relationship and some are negative. This is based on two hypotheses in schizophrenia, namely the neurodevelopmental hypothesis and the neurotoxicity hypothesis [1], [2], [21], [24].

The neurodevelopmental theory actually has been around for about 60 years. In her study of children with schizophrenia, Barbara Fish found a characteristic schizophrenia called pan-developmental retardation (eventually called pan-dismaturation), which is the presence of instability and variation in precocious development which plays a central role in differentiating the abnormalities associated with schizophrenia from other disorders. With the development of neuroimaging technology, Feinberg (1982) found that schizophrenia was caused by errors in synaptic pruning or synapse formation errors in adolescence[25]. Research supporting the neurodevelopmental theory found that in first episode schizophrenic patients there was a significant decline in memory and cognitive function, verbal learning, motor speed performance, and social function that increased slowly but surely [1]. In studies using the Trail Making Test - A (TMT-A) and B (TMT-B) to describe processing speed and working memory, it was found that patients who had a long DUP had worse test results. Length of DUP was associated with a greater index of cognitive impairment [24]. Research using near-infrared spectroscopy (NIRS) found a decrease in cortical activity in phonemic processes during DUP [26].

In this theory, impaired cognitive function in schizophrenic patients is largely a consequence of problems that occur during the development of cognitive function. Neurodevelopmental factors play an important role in impaired cognitive function in schizophrenic patients [2]. The stress or humiliation that occurs during development will cause subclinical changes in nerve cells that increase susceptibility to disease in adulthood [27]. The length of the DUP does not affect the degree of severity of cognitive dysfunction that occurs due to. This is because psychotics interfere with cognitive development at the point where they occur. Disturbances at this point will continue to disrupt further developments, precede psychotic disorders by reaching full threshold values, and are relatively stable markers of disease so that there is no effect DUP will last for a short time or for a long time. But there are exceptions to the domain of planning or problem solving. The domain of planning and problem solving belongs to advanced cognitive function, whose processes are located in the prefrontal lobe. Prefrontal lobe maturation and advanced cognitive function will continue into the mid-twenties. Psychotic symptoms will interfere with the maturation process. The more severe the disturbance during the neurodevelopmental period, the worse the prognosis is. For this reason, advanced cognitive dysfunction may become more pronounced in the period several years prior to the first episode of psychosis [2], [28]. DUP is not associated with cognitive or social functioning but its clinical effects cannot be ignored.

Research supporting the neurotoxicity theory suggests that length of DUP is associated with decreased cognitive function in general. This is because psychotic conditions can be toxic to nerves, although the mechanism of their occurrence cannot be determined. Neurotoxicity develops after sustained neuron overstimulation. Psychotics cause disruption in the release of presynaptic dopamine in the limbic striatum, resulting in prolonged endogenous neurochemical overstimulation and changes in neuronal structure[29]. Psychotics result in initial insults that can alter cellular function and make the system vulnerable to subsequent insults or psychotics progressively result in loss of normal cellular function with additional humiliation, where the effect of one insult in isolation is not sufficient to cause illness [27]. Other theory states that active psychotics are neurotoxic possibly due to psychotic processes reducing neuronal connectivity. The neurotoxicity process will lead to stress and stress-related hormones release, both of which can lead to alteration in brain structure and function [29].

This association is stronger in patients having low IQ in their premorbid periods because IQ is neuroprotective. This neuroprotective role occurs because in patients with good cognitive function allows him to endure greater deterioration before symptoms of cognitive decline become evident. In addition, good cognitive function in the premorbid phase has a higher threshold value for cognitive decline when compared with patients with poor premorbid cognitive function. Several studies have shown that a long DUP will decrease the volume of grey matter in the brain, especially in the temporal lobe. This decrease in volume describes nerve damage due to psychotic conditions

that are left without treatment, which results in decreased cognitive function of the patient [21].

When viewed from the schizophrenia onset, the acute-onset group had a shorter DUP than the insidious-onset group. This is because families are more aware of the acute-onset group. In the insidious-onset group, length of DUP showed a strong connection with cognitive function, quality of life, and social functioning. We can use DUP and negative symptoms as significant predictors of the cognitive function of patients [23]. Shorter periods of illness, higher rates of partial and complete remission, and lower rates of suicide attempts occur in patients with short DUP (<6 months). While lower mean total GAF scale scores and higher rates of single-handed living occur in patients with a long DUP (> 6 months). In addition, long DUP is also associated with the severity of negative symptoms and general mental status as well as a longer period of illness [4].

Human disease is a consequence of many risk factors occurring together over time. From the description above, it can be seen that neurodevelopmental disorders play a role in cognitive dysfunction in schizophrenia, especially in the pre-morbid period and this decline in cognitive function especially increases gradually in schizophrenia that occurs in the first two decades of life. However, the neurotoxicity theory also cannot be ruled out by looking at the functional decline in patients who have had schizophrenia for many years. Cognitive decline in schizophrenia is associated with diseases both before and after the onset of psychotic symptoms that can lead to neurogenerative changes [30].

Up to now, research into the causes of cognitive dysfunction in schizophrenia and its relationship to DUP is still ongoing. Despite differences of opinion about the impact of DUP on cognitive function in schizophrenia, early intervention in schizophrenic patients is important because DUP is associated with worse general disease symptoms, lower likelihood of remission, more severe positive and negative symptoms, and worse social functioning and overall outcomes.

SUMMARY

Cognitive impairment in schizophrenic patients has a significant impact on the degree of individual functioning and affects the quality of life. From biochemical factors, there are disorders of several neurotransmitters that underlie schizophrenia, where these neurotransmitters also affect individual cognitive function. Duration of untreated psychosis (DUP) is defined as the duration or period from the first onset of psychotic symptoms to the initial adequate antipsychotic therapy.

There are differences of opinion about the impact of DUP on cognitive function in schizophrenic patients. (1) the neurodevelopmental hypothesis says there is no impact of the length of DUP on the cognitive function of schizophrenic patients; (2) the neurotoxicity hypothesis says the length of the DUP will impact the patient's cognitive function. Despite differences of opinion about the impact of DUP on cognitive function in schizophrenia, early intervention in schizophrenic patients is important because DUP is associated with worse general disease symptoms, lower likelihood of remission, more severe positive and negative symptoms, and worse social functioning and overall outcomes. Some of the factors that cause DUP to be longer include low cognitive function, low perceptiveness, negative symptoms, minimal positive symptoms, the onset of schizophrenia, culture and religion, and substance abuse.

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