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Literature Review

Antipsychotic-Induced Dopamine Receptor Supersensitivity and Its Clinical Implications

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ABSTRACT

Introduction: Schizophrenia is a serious mental disorder that requires multi-modal and continuous treatment, mainly with antipsychotics. Along with the increasing life expectancy of schizophrenic patients, various problems due to prolonged blocking of dopamine receptors have emerged, especially dopamine receptor supersensitivity and its clinical implications. Given their chronic nature, it is often necessary to give schizophrenia patients long-term antipsychotics. Prolonged blocking of D2 receptors can result in various unpleasant effects, including dopamine receptor supersensitivity. **Review:** This phenomenon can cause problematic implications such as dopamine supersensitivity psychosis, treatment-resistant schizophrenia, and tardive dyskinesia. The risk of these side effects arises if antipsychotic use is not done wisely, such as the use of higher-than-recommended doses, antipsychotic polypharmacy, improper indications, and only relying on antipsychotics without maximizing the role of other therapeutic modalities. **Conclusion:** Clinicians need to pay attention to the rationality of the use of antipsychotics and conduct intensive supervision to reduce the risk of any clinical implications of dopamine receptor supersensitivity.

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Introduction

Schizophrenia is a form of serious mental disorder that requires long-term and comprehensive therapy [1]. One of the main modalities in the management of schizophrenia is the administration of antipsychotics from the dopamine receptor antagonist class. As the life expectancy of schizophrenic patients increases, several problems related to the long-term effects of antipsychotics have begun to emerge. The block of dopamine receptors by antipsychotics in the long term will trigger dopamine receptors to increase their affinity for dopamine, as a compensation mechanism from the body. This phenomenon is called dopamine receptor supersensitivity. This condition can lead to increased physiological responses, behavioral responses, and biochemical responses that are more than usual when the receptors encounter dopamine [1]. When the body is no longer able to compensate, this phenomenon will cause significant clinical implications that have the potential to become a problem for sufferers, such as the occurrence of Dopamine Supersensitivity Psychosis (DSP), tardive dsykinesia, and treatment-resistant schizophrenia [2].

The risk of clinical implications of dopamine receptor supersensitivity increases if the administration of antipsychotics is not prudent, such as the use of higher than recommended doses [3], inappropriate indications [4], and the increasing use of polypharmacy antipsychotics [5]. Data from WHO also shows that 50% of drug use worldwide is still irrational [6]. Clinicians need to be careful and carry out comprehensive periodic supervision in administering long-term antipsychotics to schizophrenic patients, to minimize the risk of complications that can arise due to the phenomenon of dopamine receptor supersensitivity.

Aims

Given their chronic and relapsing nature, clinicians often have to administer antipsychotics, either alone or in combination, over a long period of time to schizophrenic patients. This prolonged blockade of dopamine receptors can trigger various physiological responses as a form of compensation, one of which is an increase in the affinity of D2 receptors for dopamine. If the body is no longer able to compensate, various clinical implications can arise which can become a problem. This literature review aims to determine more clearly the pathophysiology of long-term antipsychotic-induced dopamine receptor supersensitivity and its clinical implications, as well as how the factors of antipsychotic use patterns increase the risk of this phenomenon.

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 2000-2019 issue in any research design. We also used textbooks published in the last 10 years that were related to the writing theme. Our searches are primarily on the pathophysiology of antipsychotic-induced dopamine receptor supersensitivity and it's clinical implications. However, journals about antipsychotic use patterns were also included to determine strategies for rational use of antipsychotics in order to minimize the risk of antipsychotic-induced dopamine receptor supersensitivity.

Review

Schizophrenia is a chronic mental disor-

der characterized by disharmony in the elements of thought processes, affect, emotions, volition, and psychomotor, which are reinforced by other secondary symptoms [1]. The prevalence of schizophrenia in general is estimated at 1%, which means that 1 person in 100 people will experience schizophrenia in their lifetime [1, 7]. It has been postulated that schizophrenics experience hyperactivity in the dopaminergic system in their brain [1, 8], either because more dopamine is released at the synaptic cleft, as well as increased expression and sensitivity of the D2 receptor, the receptor that plays a major role in the pathophysiology of schizophrenia [9, 10], and known as dopamine theory of schizophrenia. Based on the dopamine theory, the administration of antipsychotics from the dopamine receptor antagonist class has been shown to be useful in relieving the symptoms of schizophrenia. However, management of schizophrenia can not only be done with one modality, but includes many modalities which ideally should be implemented in an integrated and proportional way so that it can produce effective results.

Given it's chronic and recurrence nature, long-term administration of antipsychotics in schizophrenic patients is not uncommon. In some cases, antipsychotics are even given for life. Long-term use of antipsychotics can cause dopamine receptor supersensitivity phenomena, namely an increase in physiological responses, behavioral responses, and biochemical responses from dopamine receptors after binding to dopamine agonists [2].

The mechanism for dopamine receptor supersensitivity is based on the up-regulation of dopamine D2 receptors due to chronic blockade by antipsychotics, as an attempt to maintain a normal dopaminergic response [2, 7]. This up-regulation includes 2 processes, namely an increase in the affinity and density of the dopamine D2 receptor, as well as an increase in post-synaptic dopaminergic signaling through modification of the proteins and enzymes involved.

The affinity of dopamine receptors, especially D2 receptors, for dopamine agonists plays a major role in the response that occurs. Like other receptors, the D2 dopamine receptors can be available in a high-affinity state, called D2high, and a low-affinity state, called D2low. D2high receptors have a higher affinity for dopamine than D2low receptors. Both types of receptors are in an equilibrium state, to get the normal response desired [11]. The administration of antipsychotics will modify the post-synaptic dopaminergic signal cascade by modifying the proteins and enzymes that play a role therein. It has been shown in studies and animal trials that the proportion of D2high receptors compared to all D2 receptors increases as a result of this cascade change. Thus, in general, the affinity of the D2 receptor will increase [11], and then trigger a post-synaptic dopaminergic response that is higher than normal [12].

Long-term antipsychotic treatment will also increase the overall density of dopamine receptors, particularly in the striatum, either by increasing synthesis, decreasing it's degradation, or both [2]. Kostrzewa et al added that supersensitivity can occur due to the emergence of new chemoreceptors in areas where these receptors were not previously found [13]. Prolonged blockade of the dopamine D2 receptor by antipsychotics will cause the post-synaptic nerves to synthesize more D2 receptors to compensate for maintaining a normal post-synaptic response [2, 12].

Apart from the increased affinity and

density of the D2 receptor, modifications occur to the enzymes and proteins involved in the post-synaptic signaling cascade. The processes that occur are quite complex and are related to one another so that changes in one cascade chain will affect the next link. The modification that occurs will cause amplification of the dopaminergic signal and then will increase the post-synaptic response [11]. Further research is needed to obtain more complete data on the role of each protein and enzyme involved in the dopaminergic signaling cascade.

There are several factors that can influence the emergence of dopamine receptors supersensitivity induced by antipsychotics. Each of these factors is said to be unable to work alone, but requires the interaction of several factors that work simultaneously to cause this effect. These factors are genetic polymorphisms of the D2 receptor [11], types of antipsychotics [2, 11, 14], doses of antipsychotics [14], duration of administration of antipsychotics [15], as well as the use of antipsychotics polypharmacy [11, 16]. The greater the dose used and the longer the antipsychotic administration, the higher the potential for dopamine receptor supersensitivity.

When the body is no longer able to compensate, this phenomenon will cause significant clinical implications that are potentially problematic for sufferers [2, 12] including:

Dopamine Supersensitivity Psychosis (DSP)

Dopamine Supersensitivity Psychosis (DSP) is a psychotic condition caused by the phenomenon of dopamine supersensitivity [2, 11]. There are several clinical symptoms that form the basis for the diagnosis of Dopamine Supersensitivity Psychosis (DSP), namely the appearance of psychotic symptoms that are often worse, immediately after discontinuation or a sudden decrease in the dose of antipsychotics or commonly called Rebound Psychosis, the emergence of tolerance to antipsychotics, the appearance of tardive dyskinesia, increased susceptibility to stress in inducing schizophrenia symptoms, and exacerbation of psychotic symptoms after switching dopamine agonist to partial agonists such as aripiprazole.

Tardive Dyskinesia

Tardive dyskinesia is a classic symptom of the phenomenon of dopamine receptor supersensitivity that often occurs as a result of long-term administration of antipsychotics [11], especially in the typical or first-generation antipsychotic group with a prevalence reaching 20-30% [1]. The spectrum of symptoms of tardive dyskinesia includes stereotypes, dystonia, akathisia, tics (tardive tourettism), myoclonus, tremors, or chorea [1].

Treatment-resistant schizophrenia

Treatment-resistant schizophrenia is defined as schizophrenia that does not respond to improvement with a period of administration of at least 2 types of antipsychotics from 2 different groups with adequate doses and times of administration. One of the 2 drugs is not Clozapine [17]. One of the mechanisms underlying the development of tolerance which is the main feature of treatment-resistant schizophrenia is the phenomenon of dopamine receptor supersensitivity [2].

Long-term use of antipsychotics without adequate monitoring and evaluation, can increase the risk of dopamine receptor supersensitivity and all its clinical implications. The author summarizes several problems that can increase the risk of this phenomenon, which are as follows:

Use of Antipsychotic Polypharmacy

It is estimated that 40% of schizophrenics receive antipsychotic polypharmacy [5]. Faries et al also noted that many clinicians continued to use polypharmacy after complaints had improved, even though it was initially planned on a temporary basis [18].

Use of High Doses of Antipsychotics

Dickey et al reported that about 40% of first-episode schizophrenics received a dose that was higher than the recommended range in the guideline [3]. Although in some cases this can be justified clinically, if this pattern is continued without sufficient consideration, there is a risk of developing dopamine receptor supersensitivity and its clinical implications.

Use without clear indication

Research conducted in primary health care in the United Kingdom states that more than 50% of patients receiving first-generation antipsychotics are not patients diagnosed with schizophrenia or bipolar disorder, but are divided into diagnoses of anxiety disorders, depression, dementia, sleep disorders, and personality disorders [19]. This can have a higher risk of side effects, especially if given long term.

Only Rely on Antipsychotics, Without Handling Holistically

Therapists who rely solely on antipsychotics without fixing other factors, can be trapped in using antipsychotics in a prolonged, increasing dose or using polypharmacy that can be avoided.

Based on this, clinicians need to make efforts in schizophrenia therapy, to minimize the risk of dopamine receptor supersensitivity. The author summarizes several efforts that can be made, including:

Rational Use of Antipsychotics

As with other medicines, the use of psychopharmaceuticals, especially antipsychotics, must be rational. The rationale for drug administration includes proper dosage [20], proper indication [21], and minimization of polypharmacy use [22]. The use of polypharmacy antipsychotics must also be accompanied by close monitoring, given the greater risk of side effects [23, 24]. Rational administration of antipsychotics will minimize the emergence of antipsychotic-induced dopamine receptor supersensitivity.

Holistic Schizophrenia Management

Often clinicians are stuck with the pattern of increasing the dose of antipsychotics given, or adding to the combination of other types of antipsychotics, when feeling frustrated with symptoms that do not improve or social function that does not improve. In fact, not all symptoms need to be treated with increased doses of antipsychotics. Therefore, holistic management of schizophrenia, including biopsychosociocultural aspects, is needed [1, 10]. Thus, the use of antipsychotic polypharmacy in high doses can be avoided.

Handling the Clinical Implications of Dopamine Receptor Supersensitivity

In some cases, even though all precautions have been taken, clinical implications due to the phenomenon of dopamine receptor supersensitivity remain and become a problem for schizophrenics. For that, it needs proper evidence-based handling, according to the existing guidelines

Conclusion

Long-term administration of antipsychotics to schizophrenics can lead to the phenomenon of dopamine receptor supersensitivity and all its clinical implications. This risk can increase if the administration of antipsychotics is not carried out wisely and carefully, especially in the use of high doses and the use of poly pharmaceuticals. The strategy that can be done to minimize this risk is how clinicians can

give antipsychotics rationally, by taking into account all therapeutic modalities, besides the use of antipsychotics, to support recovery. If the clinical implications due to the supersensitivity phenomenon of dopamine receptors still appear after several preventive steps are taken, the symptoms that appear can be treated according to existing guidelines.

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