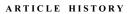**REVIEW ARTICLE**

Recent Discussions on Dopamine Supersensitivity Psychosis: Eight Points to Consider When Diagnosing Treatment-Resistant Schizophrenia

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Abstract: Dopamine supersensitivity psychosis is a clinical concept characterized by an unstable psychotic state and tardive dyskinesia in schizophrenia patients at the chronic stage. This state is thought to be induced by compensatory upregulation of dopamine D2 receptors, which is provoked by long-term and/or high-dose medications. Recent clinical data suggest that patients who responded well to medication but later exhibit dopamine supersensitivity develop tolerance to antipsychotics' effects and eventually transit to treatment-resistant schizophrenia, indicating that dopamine supersensitivity could be an etiology contributing to treatment-resistant schizophrenia. However, clinicians and researchers consider dopamine supersensitivity psychosis a minor phenomenon during the clinical course and do not make much of it. This opinion is often based on numerous clinical data indicating that dopamine supersensitivity psychosis is a relatively rare event. This review examines the data dealing with dopamine supersensitivity with the five themes of frequency, severity, withdrawal studies, switching to aripiprazole, and tardive dyskinesia. These effects of these themes on discussions of the clinical meaning of dopamine supersensitivity psychosis are then reviewed. The present review will help clinicians speculate about the background of severe psychopathology in a given patient; to make diagnoses of treatment-resistant schizophrenia and dopamine supersensitivity psychosis; and plan antipsychotic medication regimens with the goal of achieving better long-term prognosis.

Keywords: Antipsychotic, dopamine, dopamine partial agonist, tardive dyskinesia, receptor, relapse, withdrawal.

1. INTRODUCTION

1.1. Antipsychotic Medication and Treatment-Resistant Schizophrenia

The diagnosis of Treatment-Resistant Schizophrenia (TRS) is usually made when the affected individual's positive symptoms do not respond sufficiently to standard pharmacotherapy with at least two classes of antipsychotic agents [1, 2]. Several diagnosis criteria of TRS have been proposed, but all of these criteria commonly focus particularly on positive symptoms; symptoms domains other than positive symptoms are sometimes more severe in patients with TRS compared to patients with non-TRS [3, 4]. The etiology of TRS has not been fully understood, but it is considered that multiple genetic and environmental factors contribute to the development of TRS. These relevant factors are generally quite complex in a given subject, and no specific clinical factors other than positive symptoms have been identified to explain well the complete clinical picture of refractory patients [5].

Antipsychotics could be a factor relating to the refractoriness of schizophrenia. This topic has been discussed since an earlier era of antipsychotics [6]. To date, several meta-analyses of volumetric studies using Magnetic Resonance Imaging (MRI) indicated that antipsychotics' impacts on patients' brain volume, but the effects are subtle and limited to certain parts of the brain [7, 8]. However, this evidence might not indicate that the effects of antipsychotics on the brain are only slight; rather, they may only reflect the difficulty in reaching a firm conclusion on this issue. It is a fact that patients with schizophrenia show more rapid progression of brain volume reduction relative to subjects without psychiatric disorders, but it is difficult to separate the effect of antipsychotic(s) and the effects of aging and disease progression on brain volume [9]. The issue of whether antipsychotics have negative impacts on the brain structure and function of patients with schizophrenia has not reached a decisive conclusion.

To date, the class(es) and dosage thresholds of antipsychotics leading to poor long-term clinical courses in schizophrenia have not been established, although atypical an-

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tipsychotics might be more advantageous compared to typical antipsychotics in terms of some symptom domains such as negative symptoms and cognitive impairments, and less adverse events such as extrapyramidal symptoms [10-12].

1.2. Concept of Dopamine Supersensitivity Psychosis

Dopamine Supersensitivity Psychosis (DSP) is the central issue of this topic, *i.e.*, the question of whether an antipsychotic itself has a negative impact on the long-term prognoses of patients with schizophrenia. DSP is a clinical concept characterized by an unstable psychotic state observed in patients exposed to long-term and high-dose antipsychotic agents. DSP was first proposed by Chouinard and his colleagues [13, 14] and has sometimes been addressed from an iatrogenic aspect [15]. The research diagnostic criteria proposed by Chouinard [16] defined this state as a rapid exacerbation of psychosis following the tapering-off, withdrawal, or switching of one or more antipsychotics (*i.e.*, rebound psychosis: an exacerbated episode of psychotic symptoms occurring within 6 weeks for an oral antipsychotic (or within 3 months for a long-acting injectable) following tapering-off, discontinuation or switching of antipsychotic) and a gradual transition to a state of tolerance to the effects of antipsychotic(s) (*i.e.*, a clinically meaningful response to antipsychotic medication before, but afterward little response regardless of the same dosage or even higher dosage). Tardive dyskinesia (TD) is a representative neurological sign of the Dopamine Supersensitivity (DS) of Dopamine D2 Receptors (DRD2s) in the striatal region and is often classified as part of the DSP state. Chouinard initially named this 'neuroleptic-induced supersensitivity psychosis' [13, 14]. Afterwards, numerous studies, most of them in animals, demonstrated that compensatory upregulation and the supersensitivity of DRD2s that developed due to a blockade by antipsychotic(s) played a primary role in the above-described phenomena [17-23], and based on these accumulated findings, they Iyo *et al.* renamed this concept 'DSP' [24].

Since the publication by Chouinard and Jones [14], several researchers proposed the concept of DSP [16, 25-28], and only two teams defined the research diagnosis criteria [16, 26, 27]. Although these criteria and concept of DSP were not completely identical, they commonly considered that DSP appeared in schizophrenia patients under long-term treatment with antipsychotics, and that rebound psychosis, developed tolerance to antipsychotics' effects and TD are the core elements of DSP. To date, however, detailed points (*e.g.*, the numbers of symptoms and the contents of previous medications-dose and duration of previous medication trial-which are required to meet the criteria) have not been defined.

Although direct evidence showing the upregulation of DRD2s following the use of antipsychotics has been reported in few studies of human subjects [29], numerous animal model studies demonstrated this phenomenon [17-23]. The upregulation of DRD2s could be promoted by a higher dose of and longer-term exposure to an antipsychotic (Again, the high-dose and long-term which can cause a DS state have

not yet been strictly defined in a clinical study. However, there has been some evidence that chlorpromazine-equivalent [CP-eq.] 600 mg or greater for dose and at least several years for treatment duration are sufficient to provoke DS or DSP. Please see section 2. The receptor profile of each antipsychotic with tight binding with DRD2s could also influence the development of their upregulation, although agents with a relatively loose binding profile such as olanzapine can also result in DRD2 upregulation [20]. In addition, the withdrawal of an administered antipsychotic leads to behavioral supersensitivity (which has been observed after administration of psychostimulant drugs such as methamphetamine and quinpirole), and this abnormality is further promoted at roughly a week after the withdrawal of the antipsychotic, which is similar to the rebound psychosis that is often observed in patients with schizophrenia [20]. In animal studies, this phenomenon was observed in the case of continuous administration of an antipsychotic agent (*i.e.*, without withdrawal) [20, 30-32].

1.3. One of Recent Articles on Dopamine Supersensitivity Psychosis

However, there are recent reviews on TRS discussing that DSP is not likely to be important as the etiology of the disease [33, 34]. Even articles discussing the merit-demerit balance of the long-term use of antipsychotics note that DSP has been one of the leading problems with a potential negative impact on the clinical course of patients with schizophrenia, but the articles' authors raised some cautions regarding DSP [35, 36]. These four review articles dealt with the DSP theory, but they concluded that the DSP theory was not based on reliable evidence. This point of view seemed to be derived mainly from two ideas: (1) the accumulation of clinical findings suggesting that DSP is a minor (not major) problem in schizophrenia patients, and (2) the lack of direct evidence showing the increase in DRD2s in the brains of patients with schizophrenia. These are major and clear limitations of applying the DSP theory to all TRS patients, but there are some misunderstandings concerning DSP.

DSP presents with a wide variety of symptomatic forms in schizophrenia patients, but relatively simple diagnostic criteria converge for the definition of DSP. Importantly, DSP may be disregarded by clinicians when its presenting symptoms are subtle, and it can be confusing to classify a patient's symptoms as DSP (which is induced by medication) or as the disease itself when the symptoms are severe and unstable. Moreover, DSP often presents with a latent state; this state is called 'covert DSP' [14, 26], but it might be more appropriate to call it a latent (or covert) DS state instead of a form of psychosis. We suspect that clinical studies trying to capture DSP phenomena need study design that fully captures multiple forms of DSP in the broader clinical situation.

Abundant findings on the upregulation of DRD2s and the accompanying behavioral abnormalities in animal model studies may imply that more patients who are treated with an antipsychotic developed DS than clinicians have thought, even though these patients did not show a prominent episode

of DSP in their past treatment course. However, most of the discussions about TRS and most of the guidelines regarding treatment for schizophrenia have disregarded or not seriously regarded DSP and similar relevant phenomena from the perspective of etiology, symptomatology, or psychopharmacology. We suspect that this trend of viewing DSP as a minor phenomenon in clinical practice was based on the concept of DSP that has prevailed with some confusion among clinicians and researchers: that is, the view that DSP is a minor subtype among schizophrenia patients and/or TRS patients, or that DSP is an unestablished concept since there ha is no evidence of DSP in the brains of patients.

The present review will discuss several issues related to DSP that may help clear up the confusion. Molecular-level changes and abnormalities in the brain which might be caused by antipsychotic treatment, including the question of whether DRD2s truly are increased in the brains of patients with schizophrenia under treatment with antipsychotic(s), are not discussed herein. This is because gaining an understanding of DSP theory is useful when treating schizophrenia patients without DSP as well as patients with DSP [37-41]. A more concise understanding of the phenomena underlying DSP is clearly important, and unknown mechanisms other than the upregulation of DRD2s may be involved in these phenomena. These other mechanisms might be related to presynaptic dopamine dysregulation, and/or to the dysregulation of a second-messenger signal cascade following dopamine-DRD2 binding in post-synaptic neurons and that of other neurotransmitters such as 5-HT, glutamine, and GABA [42-44].

However, the findings from the latest basic neuroscience research in the relevant areas are still far away from being applied in clinical practice. We propose that there is significant merit to the DSP theory because it encourages a reconsideration of the theoretical background of patients' unresponsiveness to antipsychotic treatment, perhaps enabling optimal changes in treatment strategies and overcoming the serious psychotic symptoms in the patients. To present these merits, we review the five topics that should be addressed in discussions of the issues concerning DSP and TRS (frequency, diagnosis, withdrawal study, action of aripiprazole, and TD will be discussed one by one). These topics can be reviewed because substantial data from multiple studies of each topic have been collected, but those studies did not seriously consider (or disregard) DSP and DS in their study design or discussion of findings or both, or some of the topics were discussed separately without considering the connections among them. This can result in an underestimation of the significant position of DSP.

To this end, the PubMed database was searched for relevant English literature up to May 2020. We used search terms such as "dopamine supersensitivity (psychosis)", "rebound (psychosis)", "withdrawal (psychosis)", "relapse", "(tardive) dyskinesia", "extrapyramidal symptoms" "treatment-resistant (schizophrenia)", "antipsychotic", "long-term treatment", "adverse event", "side effect", "dopamine D2 receptor", "haloperidol", "clozapine", "long-acting in-

jectable", "aripiprazole", and "brexpiprazole". We then read the manuscripts yielded by the PubMed search and examined how they deal with topics relevant to DSP. We are very interested in how the researchers in this field deal with and discuss DSP, rather than in a systematic meta-analysis, and thus our search methods did not cover all the relevant literature.

2. THE FREQUENCY OF DSP AMONG PATIENTS WITH SCHIZOPHRENIA

The contention that patients with DSP are a minor subtype in schizophrenia or TRS may be based on the findings from several studies that reported a not very high rate of DSP in the studied cohort. Accumulating evidence showed that approx. 30% of patients with schizophrenia develop TRS throughout treatment [1, 45]. More recent long-term (> 5 year) follow-up studies suggested that patients who develop TRS after exhibiting DS induced by treatment with antipsychotic(s) at the initial stage could be a minor group among the entire population of TRS patients. Lally *et al.* [46] conducted a 5-year longitudinal study of 246 patients with First-Episode Psychosis (FEP), and they reported that at the final assessment point, 81 of the patients (33.7%) eventually fulfilled the TRS criteria. In addition, 56 of the patients who developed TRS (70%) did not achieve a state of remission at all, and they met the TRS criteria at various time points during the 5-year observation period. Similarly, Demjaha *et al.* [47] followed a total of 323 patients with FEP for 10 years, and they observed that 74 patients (23%) met the TRS criteria at varying timepoints during the 10-year observation, and 62 (84%) of the TRS patients did not experience symptomatic remission at all. The two studies strongly suggest that a majority of TRS patients might have been vulnerable to TRS from their early stage of disease (this type of TRS is called 'early-onset TRS' in both studies). Based on these findings, some researchers concluded that patients with DSP or late-onset TRS are simply a minor subtype of TRS patients [33]. These two studies provided a quite important classification of TRS into early-onset and late-onset TRS, but this classification might be insufficient when taking DSP more into consideration. This is because there may be some early-onset TRS patients who are given high-dose treatment and subsequently develop TRS (that is, patients having the pathologies of both early-onset and late-onset TRS. Please see section 3.).

However, the development of DSP needs a much longer period of treatment with antipsychotic(s), since typical DSP signs or symptoms are generally observed in patients at the chronic stage of the disease **Point 2**, Table **1**. In animal models (usually rodents), the administration of haloperidol for only 14 days generally establishes the DS state, but in human subjects, it is not yet known how long antipsychotic treatment is necessary for the development. Chouinard *et al.* examined 224 patients (average age > 40 years old; average dose of antipsychotic(s) > 700 mg of chlorpromazine-equivalent [CP-eq.] dose), and 97 patients were classified as having DSP, revealing a relatively high ratio (43%) [48]. However, in the same study, 174 patients (77.7%) who were

Table 1. Crucial points that should not be neglected when Dopamine Supersensitivity Psychosis (DSP) is considered.

Diagnosis of DSP in Clinical Practice.
Point 1. DSP observed in clinical practice presents broader psychopathologies than the phenomena discussed at the receptor level (that is, development of dopamine supersensitivity).
Point 2. A diagnosis of DSP generally requires that a patient has had both high-dose and long-term antipsychotic treatment.
The sign of DSP can present covertly or overlap with original TRS symptoms.
Point 3. Among patients with DSP, there are those who meet the criteria for TRS due to severe DSP, and those who meet the criteria for TRS due to DSP and originally TRS that had existed from the beginning of schizophrenia.
Point 4. There are patients who develop latent DSP (covert DSP). (But it is generally possible to identify the clinical signs of dopamine supersensitivity in patients).
Tardive dyskinesia
Point 5. Tardive dyskinesia is a strong sign of the development of dopamine supersensitivity. This phenomena can exist covertly during on antipsychotic treatment and can fluctuate or be masked under rebound psychosis.
Cautions to interpret opinions depending on previous findings since clinical practice and clinical studies are different in terms of patients' background and treatment condition.
Point 6. The frequency of DSP varies greatly depending on the background of the patients and past/present treatments in addition to the methodology of the study.
Point 7. Rebound psychosis is generally included in relapse, but the reverse is not true. The withdrawal study prospectively observing relapse following the intentional withdrawal of antipsychotics might not count true rebound psychosis. This can overlook rebound psychosis or include true relapse irrelevant to the withdrawal.
Point 8. Worsening psychosis following switching to aripiprazole is the best indicator of dopamine supersensitivity. This phenomena can be influenced greatly by the background of patients and the switching method.

classified as not having DSP had been treated with a lower CP-eq. dosage of antipsychotics (average 472 mg). We reported that 72% of 147 TRS patients with approx. 20-year treatment histories had experienced at least one DSP episode, and they had been treated with high-dose antipsychotics, *i.e.*, CP-eq. 770 mg [49]. We observed in another study that a majority of non-TRS patients (79.4%) had not had any previous DSP episode, and this group had been treated with relatively low antipsychotic(s) of CP-eq. doses at 452 mg [50]. The data from these two research groups indicate that DSP appeared at a relatively high frequency among patients at the chronic stage of the disease and that DSP was linked to high-dose antipsychotic treatment in addition to long-term treatment. The medication states in these studies [49, 50] were very similar in terms of antipsychotic dosage and treatment duration, which were apparently higher and longer than those in the Lally *et al.* [46] and Demjaha *et al.* studies [47].

Even though researchers directly checked DSP episodes, some earlier studies might disregard them due to relatively short-term observation. For example, a study reported that only 12 patients among a total of 265 experienced a rebound psychotic episode [51]. That study's patients were followed for only 3 years, and DSP episodes before and after this short period might have been missed. In addition, the study did not show the data of the medical states (antipsychotic treatment and duration of illness) of the patients judged as the no DSP-type group, and it was thus unclear what type of patients and what levels of severity of schizophrenia were included **Point 6**, Table **1**. On the other hand, in a study by Fallon and his colleagues [27], 39% of the relapses of 41 patients met the criteria for DSP, based on the careful observation of stress vulnerability and TD.

When a given patient maintains the same drug regimen with a good adherence level, DS that has developed could be masked since rebound psychosis scarcely occurs (covert DSP) [15] **Point 4**, Table **1**. Accordingly, the estimations of the rate of DSP could be greatly affected by the observation methodology (*e.g.*, a retrospective or prospective design, and the duration subjected to study), the treatment setting (outpatients, inpatients or both), and the definition of the key concepts for the diagnosis (relapse, DSP or TRS).

The rate of DSP could also differ among regions. It has been pointed out that, particularly in Asian nations, antipsychotic polypharmacy has been administered to many patients [52, 53]. In Japan, clozapine became available to clinical practices in 2009; polytherapy with typical antipsychotics was common before 2000, and polytherapy with both typical and atypical antipsychotics has been common since then. The pharmaceutical and medical scenarios in specific countries and regions could lead to results at high or low rate of DSP.

It may also be necessary to examine this issue from the viewpoint of sex, *i.e.*, the difference between male and female patients. Epidemiological data suggest that male patients tend to experience the onset of schizophrenia earlier and go on to experience a slightly worse prognosis compared to female patients [54]. It has been speculated that these differences are related to favorable effects of female hormones or the higher transition rate from autistic spectrum disorder to schizophrenia in male patients [55]. To date, however, there have been no data examining the relationship between sex and DS/DSP.

3. DIFFICULTY IN DISTINGUISHING BETWEEN TOLERANCE TO THE EFFECTS OF ANTIPSY-CHOTICS AND THE NEUROPROGRESSIVE PATH-WAY TO TRS

3.1. Grade of Rebound Psychosis Depending on Developed Dopamine Supersensitivity

Since it is difficult to treat severe rebound psychosis appropriately, it is difficult to judge whether it should be recognized as DSP or as part of the process of developing TRS or both. There has been little discussion on the potential relationship between emergence of rebound psychosis and TRS [56, 57].

As a result of the blockade of DRD2s by high-dose and/or long-term antipsychotic treatment, primarily a compensatory increase in the density of DRD2s (*i.e.*, up-regulation) and/or acquired supersensitivity of the receptors are involved in rebound psychosis [24]. In DRD2-supersensitive brains, if antipsychotic(s) are withdrawn from the DRD2s for various clinical reasons such as treatment withdrawal, tapering-off, or switching an ongoing antipsychotic regimen, endogenous dopamine binds with available DRD2s and stimulates them, leading to worsened psychosis. In addition, rebound psychosis appears at varying intensities, which might depend on the patients and clinical situations **Point 1**, Table **1**. This form of rebound psychosis could be classified into the following three forms based on the intensity.

The mildest form of rebound psychosis appears at somatic and/or physiological levels such as nausea, anxiety, insomnia, restlessness, and hyperarousal. These symptoms generally appear temporary, and it may thus be incorrect to consider this from rebound "psychosis". The phenomena in this form are interpreted as the signs of a process of physiological adjustment from the long-term situation with the complete blockade of DRD2s to the new situation with less blockade. This process is similar to the cases of benzodiazepine and antidepressant withdrawal [58, 59].

The next form of rebound psychosis has a more severe etiology and presents with exacerbations of delusions and hallucinations. These positive symptoms are usually the same as the patient's original psychotic symptoms. In most cases, the rebound psychosis starts to appear within a relatively short period (generally a few days to a couple of weeks) immediately following the discontinuation, dosing-down, or switching of ongoing antipsychotic(s). This form of rebound psychosis usually recovers quickly with the reinstatement of the prior medication [16, 58, 60].

The most severe form of rebound psychosis shows resistant symptoms against a further increase in antipsychotic(s) and presents with irreversible psychotic symptoms. Certain novel psychotic symptoms are sometimes accompanied by the patient's original symptoms. This state implies tolerance to the effects of antipsychotics and might be interpreted as the 'final' form of DSP. This severe form of DSP is strongly linked to the development of TRS [16]. The state is similar to treatment failure or to the development of tolerance to an-

tipsychotics observed in animal studies [20, 61-63]. However, it is uncertain whether this tolerance to antipsychotics in schizophrenia patients is completely identical to treatment failure in animal models **Point 1**, Table **1**. It is difficult to explain this severe form of rebound psychosis simply from the viewpoints of pharmacokinetics and pharmacodynamics of the withdrawn antipsychotic(s), since quite high-dose treatments providing a quite high occupancy rate of DRD2s are not effective at all against the exacerbated psychosis. It may thus be inappropriate to interpret this form as a type of rebound psychosis.

3.2. Severe Rebound Psychosis, The Treatment-Resistance Process, or Both?

The severe form of rebound psychosis can be recognized as a process shifting to TRS, irrelevant to medication. This final form of rebound psychosis is one of the most serious situations in the clinical course of schizophrenia, but it has not been examined extensively in clinical research. This is also related to the fact that relapse episodes often appear at a relatively early stage; second and third acute psychotic episodes (*i.e.*, the first and second relapses) tend to occur within a few years after the introduction of treatment for FEP [64-67]. Instability of the psychopathology at this stage could be interpreted as a continuation of the patient's FEP or a further progression of the disease itself (*i.e.*, the process of becoming refractory to TRS). During treatment at an early stage, some patients might have a concurrent DSP episode in addition to the underlying etiological process of TRS **Point 3**, Table **1**. This complex nature of the clinical state at an early stage of the disease leads to the further difficulty of determining whether a given worsening of symptoms at the early stage meets the criteria of DSP or not.

Taken the accumulated clinical findings together, it is apparent that rebound psychosis takes varying forms depending on its severity **Point 2**, Table **1**. It is reasonable to speculate that in chronic-stage patients, when a relapse appears with severe psychopathology following a relatively stable clinical course, the relapse episode includes the pathology of DSP, regardless of the presence or absence of TRS. However, milder forms of rebound psychosis without evident psychotic symptoms may be disregarded by clinicians, and the severe form can be confused with true TRS pathology irrelevant to the patient's medication **Point 3**, Table **1**. This point presents a serious and unresolved issue concerning the relationship between DSP and TRS. In DSP, while some cases have the potential iatrogenic aspect of unnecessary high-dose treatment which might be avoidable, others are treated with a high dose of antipsychotics within the standard dose range (*i.e.*, CP-eq. dose <600-800 mg) as clinically acceptable as standard pharmacotherapy. Particularly in the latter type of patients, DSP might be interpreted as 'getting stuck in the TRS etiology', in which is not possible to separate the element of DSP from the original pathology of schizophrenia. A method or concept of differentiating them-that is, the point at which DSP started or the weight that DSP carries in the entire pathology-does not yet exist.

4. STUDIES OF ANTIPSYCHOTIC WITHDRAWAL

Careful attention should be paid to several clinical trials examining the rates of rebound psychosis following the intentional withdrawal of ongoing antipsychotic regimens. This problem is related to the difficulty in determining whether the relevant rebound symptoms following medication withdrawal is a temporary phenomenon that occurs only during the metabolizing process of the antipsychotic or whether it is a trigger that revokes a true psychotic relapse [60, 68] **Point 7**, Table **1**.

Similar studies designing the withdrawal of an ongoing antipsychotic regimen reported varying rates of rebound psychosis or relapse after the withdrawal [69-71]. These inconsistent findings are related to the lack of clarity in the definition of the primary outcome (*i.e.*, worsening psychosis) in almost all of these studies. Each study did not mention which type of worsening episode (*i.e.*, redound psychosis only or both rebound psychosis and true relapse) was being examined. In addition, most of the studies used terms such as "withdrawal", "rebound", and "relapse", with no description of the specific intention as to why the study selected the term(s). The studies used these terms, but almost all of the studies seemed to include all types of worsening psychotic episodes after antipsychotic withdrawal, leading to some difficulty in understanding the authors' hypothesis on the relationship between the withdrawal of an antipsychotic agent and changes in the symptoms or clinical course. Another problem of these withdrawal studies is also attributable to the ambiguity in capturing the patients' worsening symptoms. The significant parts of the studies depended only on clinical records such as emergency hospital visits or rehospitalization information, perhaps implying only retrospective chart reviews.

When considering a study that attempted to observe symptom worsening following the withdrawal of a specific class or form of antipsychotics, readers should be very careful to identify which types of worsening of the psychosis the study observed, *i.e.*, only rebound psychosis as DSP or both rebound psychosis and natural relapse (which might be irrelevant to the withdrawal); otherwise, the interpretation of the study's data could be incorrect. For instance, when a study has tried to estimate the rate of rebound psychosis after the withdrawal of a specific agent but did not include patients who had developed DS, it is not surprising that the rate of rebound psychosis is low. In such cases, it should not be concluded that the agent caused less rebound psychosis.

Although the earlier studies examining the rate of the occurrence of symptom worsening had designs capturing all types of worsening psychosis following the withdrawal of medication, it seems that their findings suggested a high rate of rebound psychosis that was induced by the discontinuation of an ongoing antipsychotic. A meta-analysis including 4,365 patients from a total of 66 studies of the discontinuation of antipsychotic(s) indicated that 58.2% of the patients whose medication was withdrawn experienced worsening symptoms, whereas only 15.6% of the patients maintaining their medication did [72]. The studies included in that meta-analysis may not have differentiated rebound psychosis (in-duced by the withdrawal of medication) and relapse (which can occur irrelevant to the withdrawal). However, quite a few of the studies in the meta-analysis reported that over ~50% of the patients in the withdrawal group experienced symptom worsening, and these episodes occurred immediately after the discontinuation of the medication [72]. Moreover, some of these studies observed that the doses of ongoing antipsychotics prior to the withdrawals as a predictive factor of the appearance of worsening symptoms [73]. Although the meta-analysis itself did not establish the drug dosages prior to the start of withdrawals as a predictor of the consequent rebound psychosis, some of the studies included in the meta-analysis reported relatively high rates of symptoms worsening, reflecting the characteristics of rebound psychosis that could be recognized as due to the withdrawals, rather than a natural relapse.

A recent meta-analysis that obtained more data than that provided by Gilbert *et al.* [72] reported again that patients whose treatment with antipsychotics was maintained showed a lower relapse rate than those whose treatment with antipsychotics was withdrawn [74]. However, the analysis demonstrated that there was no significant difference in the relapse rate among withdrawal groups between those with rapid discontinuation and those with gradual discontinuation and that the duration of the withdrawal procedure (*i.e.*, the speed of withdrawal) did not affect the subsequent relapse rate, suggesting that the incidence of rebound psychosis was not very high in the entire relapse population of the included studies. A similar conclusion was reported from another meta-analysis [75]. Thus, these previous studies, including meta-analyses of withdrawal studies, yielded inconsistent findings, providing no definite conclusion on whether the withdrawal of antipsychotic(s) provokes a high rate of rebound psychosis, although withdrawals that included all types of symptom worsening were related to high relapse rats. These inconsistent results among studies may be attributable to a variety of factors such as the study design (*i.e.*, prospective *vs.* retrospective), the antipsychotic(s) withdrawal procedure (*i.e.*, abrupt discontinuation *vs.* gradual discontinuation), the definition of relapse, and the follow-up duration or treatment in the maintenance group [76].

In summary, a study of the intentional withdrawal of a given antipsychotic may accurately capture the rate of rebound psychosis, particularly when conducted with a prospective study design. In contrast, studies designed with the inclusion of both rebound psychosis and other patterns of symptom worsening cannot identify the occurrence rate of only rebound psychosis: the interpretation of such data requires caution. The more important factor to interpret the results is the patients' backgrounds *i.e.*, whether or not the patients have DS-rather than the class of antipsychotics studied. It is not surprising that the reported rates of symptom worsening after withdrawals have been low even for agents that have a profile that is likely to cause rebound psychosis (such as a short-half life and loose binding with DRD2s) when many patients without DS were included in the studies. When we discuss the rate of rebound psychosis or relapse, based on data from these intentional withdrawal

studies, it is not possible to do so without considering the patients' backgrounds (especially those that include developed DS).

5. THE EFFECT OF ARIPIPRAZOLE ON DSP

Aripiprazole, a dopamine partial agonist, exhibits non-inferiority to other atypical antipsychotics (except for clozapine) in the treatment of patients with schizophrenia. Aripiprazole also presents fewer risks of several types of adverse events such as extrapyramidal symptoms, metabolic syndrome, and hyperprolactinemia [77]. However, ever since aripiprazole became available for clinical use, many case reports and several studies reported that when aripiprazole was switched from another antipsychotic(s) or was added to other ongoing antipsychotic(s) in a given patient, the patient experienced a worsening of psychotic symptoms [78, 79].

In an animal model, it was demonstrated that DS established by haloperidol could be ameliorated by the administration of aripiprazole [21], although a study using young rats reported that aripiprazole caused DS [80]. However, reversal phenomena are thought to occur in humans. That is, in patients with established DS, the DRD2 partial agonist mechanism of the agent stimulates supersensitive DRD2s, resulting in symptoms worsening [24] **Point 8**, Table **1**. This theory is related to the unique characteristics of aripiprazole as dopamine partial agonist: *i.e.*, its agonistic or antagonistic function that is changeable depending on dopamine tone or available receptor reserve [81, 82]. That is, presynaptic dopaminergic neurons, not limited to post-synaptic DRD2s, might also commit to this phenomenon (worsening symptom after addition of aripiprazole) [83].

The review articles which did not consider DSP important in the etiology of TRS did not make any comments about worsening psychosis due to aripiprazole. However, this phenomenon is often observed in clinical practice [33, 34, 36]. Unfortunately, only one study examined the possibility that DS may be involved in the worsening of psychosis by the addition of or switching to aripiprazole [84]; that retrospective study of 264 patients whose antipsychotic medication was switched to aripiprazole revealed that 56 of 70 patients who were judged as having DS consequently showed a failure of the switch to aripiprazole, and 16 of the 56 patients exhibited a worsening of positive symptoms. On the other hand, the 194 patients who were judged as not having DS exhibited a very high continuous rate of success after the switch to aripiprazole, and since the worsening of positive symptoms was observed in only 16 patients, there was a significantly low rate of aripiprazole treatment drop-out compared to the patients with DS [84].

Several studies identified the following as being related to failure in switching to aripiprazole: treatment with high-dose medication [85-87], treatment over a long-term period [88], or both [89]. In contrast, patients with low-dose medication and even those with TD have been successfully switched to aripiprazole [90]. These differences in the success or failure of switching to aripiprazole may be derived from the degree of severity of DSP and the method of switching to aripiprazole. There are a few studies denying the possibility of symptom worsening by a switch to aripiprazole compared to switching to other antipsychotic(s) [91-94].

More importantly, the success/failure of switching to aripiprazole could be greatly affected by the switching methodology [95]. A rapid switch to aripiprazole, in particular, was related to higher rates of relapse and of dropping out of the study relative to add-on switching or cross-titration, as confirmed by several studies [85, 96-98], with the exception of one study [99]. The clear differentiation in symptom worsening between rapid and gradual switching to aripiprazole well reflect one of the diagnosis criteria of DSP, showing that rebound psychosis occurs when medications are rapidly withdrawn, but not when gradually withdrawn [16].

These findings from a series of studies of switching to aripiprazole indicated that a failure of switching to aripiprazole and maintaining aripiprazole after the switch could be involved in the established DS, since these worsening situations implied rebound psychosis **Point 8**, Table **1**. To the best of our knowledge, there is no reported evidence that the effects of DS on switching to oral aripiprazole could also be true of other dopamine partial agonists such as once-monthly injectable aripiprazole and brexpiprazole. However, symptom exacerbation following a switch to aripiprazole was reported to result in a typical case of rebound psychosis, and this potential outcome is emphasized in the new diagnosis criteria of DSP that are used when determining whether patients have DSP [26].

6. TARDIVE DYSKINESIA IN DSP

TD is the most representative neurological sign suggesting DS [24]. TD has been included in the research criteria of DSP [16, 26, 27]. However, several matters should be considered when TD is discussed in relation to TRS.

A small portion of patients with TD could be classified as having the intolerant type of TRS due to his/her TD itself, but this is relatively rare. This type of patients sometimes have both TD and tardive dystonia, and the latter contributes more seriously to the reduction of patients' daily functioning. It has been reported that both of these tardive syndromes can appear concomitantly in patients with each of the tardive syndromes at a relatively high rate [100].

Serious issues have been raised in the recent literature: whether DS underlies TD and whether the existence of TD as a sign of DS truly contributes to the development of TRS. This viewpoint *i.e.*, TD reflects DS was a premise of both the basic and clinical research in earlier years [101, 102], but recent findings that neurotransmitter systems other than that of dopamine could be involved in the etiology of TD seem to cast some doubt on the classical viewpoint [103]. Particularly, the role of vesicular transporters within presynaptic neurons are quite important findings, and VMAT 2 inhibitors with a relevant mechanical action are being applied to the actual treatment strategy [104-106]. In addition, sever-

al lines of evidence provided the basis of the oxidative stress theory as the mechanism of TD [107].

However, TD can arise due to treatment with typical antipsychotic(s) at a higher rate compared to treatment with typical antipsychotic(s) [15, 108]. The development of TD is related to higher-dose and longer-term treatment [109], and is temporarily effective with the addition of an antipsychotic; however, dyskinesia could be subsequently worsened [110]. TD Clozapine is highly effective for TD, possibly due to which has a loose binding profile with DRD2s with clozapine [111]. All of the above reports provide evidence that the blockade of DRD2s by antipsychotic(s) is directly related to the later occurrence of TD **Point 5**, Table **1**. Thus, the involvement of other neurotransmitter systems or mechanisms other than DS does not preclude the classical viewpoint that the DS of DRD2s underlies TD.

Another question is related to a few studies reporting that TD was not accompanied by rebound psychosis, suggesting that the former could be irrelevant to DS and TRS [112]. On the other hand, some studies contradict this; that is, TD appeared concomitantly with rebound psychosis at a relatively high rate [15, 113, 114]. This controversy can be explained in light of the following two characteristics of TD: (1) whether or not the study subjects had developed DS, which is a point similar to our previous discussion of withdrawal studies, and (2) whether TD has been established but covertly masked for a long time period [115]. That is, patient's backgrounds concerning medication (*i.e.*, established DS or not in study's cohort) or study's design concerning when TD is judged (*i.e.*, during on-medication or following medication withdrawal) can influence the study's result.

However, it remains unclear whether TD itself without rebound psychosis can lead to the development of TRS. Our previous investigations defining TD as DSP demonstrated that few subjects were classified as having DSP due to with TD and without rebound psychosis [38, 49]. Our findings indicated that the rate of TD was not so much higher in the TRS patients, regardless of high-dose treatment. If this is true, it is possible that in discussions of the contributing role of DS in the pathway to TRS, the role of TD is not equal to that of rebound psychosis, which is partly in line with the viewpoint that TD does not play a significant role in the pathology of DSP [33].

To date, there are few data regarding the concurrent emergence of TD with rebound psychosis, which may have led to an underestimation of the significance of TD when DSP are counted. An issue that remains to be addressed is the diagnostic value of TD when studying and discussing its role in the development of TRS.

CONCLUSION

The present review categorized both data dealing with DSP and data concerning the discussion about DSP based on five topics. Regarding the frequency of DSP, the follow-up or observation durations could greatly affect the frequency. Episodes of tolerance to antipsychotic effects can be con-

fused or overlapped with the inherent procession to TRS, implying the difficulty of accurately judge the potential background of the development of TRS. Almost all withdrawal studies analyzed all types of symptom worsening together (including rebound psychosis), which has led to unclear discussions about drug withdrawal and relapse. The worsening of a patient's condition after switching to aripiprazole has been suggested to be due to DSP itself, but most studies' discussions disregard this valuable and unfavorable phenomenon. TD is one of the most typical signs of DS, but the significance of TD can vary, depending on the context relating to TRS, DSP, or other extrapyramidal symptoms.

The current controversy surrounding the phenomenon of DSP may cause physicians to minimize or overlook DSP when treating their patients with schizophrenia and seems related to a general trend of holding schizophrenia patients responsible for their own disease recurrence. In addition, the ambiguity surrounding DSP as a clinical entity could make it difficult for physicians to balance their short-term and long-term goals for pharmacotherapy in their patients with schizophrenia.

Mechanisms other than those involving post-synaptic DRD2s may be involved in the etiology of DSP, and this etiology may be further overlapped with the etiology of schizophrenia itself. This complexity has led to difficulty in discussing them separately (*i.e.*, the disease itself and antipsychotic-induced DSP). TD research might help clarify mechanisms other than post-synaptic DRD2s that might be involved. In addition, the new evidence described herein does not devalue the significance of clinical DSP in consideration of the disease process and the limitations of antipsychotics' effects.

CONFLICT OF INTEREST

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