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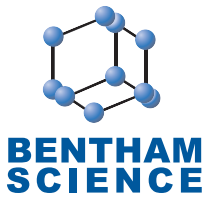

Antipsychotic Induced Dopamine Supersensitivity Psychosis: A Comprehensive Review

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Abstract: Chronic prescription of antipsychotics seems to lose its therapeutic benefits in the prevention of recurring psychotic symptoms. In many instances, the occurrence of relapse from initial remission is followed by an increase in dose of the prescribed antipsychotic. The current understanding of why this occurs is still in its infancy, but a controversial idea that has regained attention recently is the notion of iatrogenic dopamine supersensitivity. Studies on cell cultures and animal models have shown that long-term antipsychotic use is linked to both an upregulation of dopamine D_2-receptors in the striatum and the emergence of enhanced receptor affinity to endogenous dopamine. These findings have been hypothesized to contribute to the phenomenon known as dopamine supersensitivity psychosis (DSP), which has been clinically typified as the foundation of rebound psychosis, drug tolerance, and tardive dyskinesia. The focus of this review is the update of evidence behind the classification of antipsychotic induced DSP and an investigation of its relationship to treatment resistance. Since antipsychotics are the foundation of illness management, a greater understanding of DSP and its prevention may greatly affect patient outcomes.

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Keywords: Antipsychotics, dopamine supersensitivity psychosis, D_2-receptors, rebound psychosis, relapse, schizophrenia, treatment-resistance, tolerance.

1. INTRODUCTION

Schizophrenia is an incapacitating psychiatric disorder characterized by complex clusters of positive, negative, and cognitive symptoms. The worldwide prevalence estimate of schizophrenia is around 0.7-1% with an illness trajectory that is both chronic and relapse prone [1]. Despite treatments with antipsychotics being effective in curtailing acute symptoms, multiple relapses still occur frequently. The cumulative first relapse rates reach almost 80% within 5 years after initial diagnosis [2]. Generally defined as the exacerbation of psychotic symptoms after initial clinical improvement and stability, relapse and its prevention remain the essence of pharmacotherapy [3]. Even with appropriate intervention, treatment responses often wane over a longitudinal timeline. This worsening of illness severity in the context of continual antipsychotic exposure may be a sign of treatment resistance, a possible reflection of the emergence of supersensitivity at the synaptic level.

Since the discovery of chlorpromazine, the cornerstone of schizophrenia treatment has been the early and continuous use of antipsychotics. Current treatment guidelines provide evidence-based strategies for early and continual implementation of antipsychotics with the goal to mitigate the escalation of psychotic symptoms and prevent relapse [4, 5]. Despite early pharmacological intervention, there is still uncertainty with regards to the long-term effectiveness of these drugs. Indeed, one recent 20-year multi-follow-up study reported that antipsychotics might not necessarily ameliorate psychosis in patients that were continually prescribed medications [6]. The investigators noticed significantly more psychosis in patients that were persistently treated with antipsychotics than those that were not. Unexpectedly, these results suggest that long-term antipsychotic utilization might lengthen the attenuation of untoward symptoms, as not all patients seemed to have benefited from long-term treatment [7, 8].

The evidence in these non-randomized studies challenges the justification of current treatment guidelines that promote continual antipsychotic utilization for the treatment of schizophrenia. However, these studies have limitations that include the likelihood that clinicians opted for continual

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administration of antipsychotics for those individuals exhibiting more severe symptoms. Regardless of the methodological critiques, there is a shift in the focus of antipsychotic research. With chronic administration in animal studies being linked to physiological neuro-adaptations, the concept of iatrogenic psychosis has been re-accentuated [9-11]. The core of this phenomenon lies with the proposed supersensitivity of the mesolimbic dopamine system. Historically, an increase in D_2-receptor binding sites over successive increases in dosage has been suggested as a culprit as to why certain patients experience poor responses to multiple antipsychotics over time [12]. Recent publications have explored this postulation and have started to address iatrogenic dopamine supersensitivity psychosis (DSP) as a concrete issue, but should such a conclusion be made [13].

The role of antipsychotic induced DSP in treatment resistance and relapse is an idea that is often hypothesized in various clinical studies and case reports [14, 15]; however, it is routinely dismissed as an inconsequential factor in the development of recurrent symptoms [16]. For instance, previous reviews have emphasized the difficulty in establishing a causal relationship through indirect approaches, which impedes the interpretation of evidence [17]. On the other hand, refuting this concept is also challenging since there is direct support that the supersensitivity is related to the overt presence of drug tolerance [9, 18]. If supersensitivity is the mechanism for antipsychotic tolerance, then perhaps psychosis may be induced under particular situations where neurotransmitter levels and receptor density are pharmacologically altered. These arguments are just a few reasons as to why this area of research is still controversial with many contrasting viewpoints [13, 17].

In terms of diagnosable characteristics, the criteria and definition for antipsychotic induced DSP is not rigid. Certainly, clinical evidence is difficult to explicate and is not as well documented compared to preclinical animal studies. However, recent utilization of D_2-receptor partial agonists, specifically aripiprazole, has highlighted aspects of DSP with regards to treatment resistance that warrants a closer consideration of the supersensitivity phenomenon [19]. This comprehensive review explores the components of iatrogenic DSP with a focus on evaluating the evidence for this clinical syndrome. Although DSP may not be as significant in comparison as the natural progression of schizophrenia, it is possible that the involvement of DSP in treatment resistance—specifically refractory schizophrenia—has been overlooked and has a greater impact on drug therapy than previously thought.

2. BACKGROUND TO THE DSP DISCUSSION

Dopamine neurotransmission is mediated *via* five G protein-coupled receptors (GPCR) that have been categorized into two broader subtypes based on their ability to modulate cAMP production. D_1-subtype receptors (D_1 and D_5) stimulate cAMP production by activating adenylyl cyclase while D_2-subtype receptors (D_2, D_3, and D_4) inhibit adenylyl cyclase [20]. Although there is plethora of research analyzing the structure, location, and roles of all these receptors in relation to psychotic disorders, the most clinically relevant to antipsychotic induced DSP is the D_2-receptor [21, 22].

All antipsychotics act in some capacity as antagonists at the postsynaptic D_2-receptor, thereby reducing the activation of dopaminergic pathways in the mesostriatal and mesolimbic systems. Similar to other GPCRs, D_2-receptors are under dynamic regulation from many kinases and trafficking enzymes. For instance, neurotransmission can undergo both desensitization and resensitization depending on the regulatory mechanisms in play [21]. Radioligand assays using homogenized animal and human post-mortem brain tissue have also shown that receptors interconvert between two affinity states: high, coined D_2^{high} and low or D_2^{low} [23]. A favorable propensity for D_2^{high} state can lead to greater activation of dopamine receptors, an observation supported by animal studies [24]. However, the existence of these receptor states has not been conclusively proven in *in vivo* human studies making it difficult to declare causation from a purely mechanistic standpoint. Nonetheless, evidence for oscillating affinity states of D_2-receptors does suggest that receptor states can participate as a modulatory component of receptor regulation.

3. EXPLORING MECHANISMS OF DOPAMINE SUPERSENSITIVITY

Like many tightly regulated receptors in the brain, the D_2-receptor is prone to plasticity and adaptive remodeling. One recent hypothesis underlying the etiology of schizophrenia is the idea that dopamine receptors respond to defects of neural circuitries and become supersensitive as a compensatory mechanism [18]. Although far from being well-established, there is evidence to suggest that the sensitivity of D_2-receptors can be altered by many factors not limited to: neural pruning of presynaptic receptors, birth injury, gene deletions, dimerization of dopamine receptors, substance abuse, and continual administration of antipsychotics [18, 25]. Exploring further, it seems that the possible mechanism of DSP arises from a modification of the D_2 signaling cascade. Without expanding on the complex signaling networks of D_2-receptors, it is nevertheless important to note some prominent regulatory proteins.

The first type of regulatory proteins involves the promotion of GTP hydrolysis on G-protein α-subunits thereby reducing the activation interval of inhibitory G-proteins upon D_2-receptor stimulation. Aptly named regulators of G-protein signaling (RGS), genetic variations of these proteins may show a susceptibility to alterations under various stressors [26]. If the negative modulation of RGS proteins were dampened, the activation lifetime of D_2-receptors might be heightened leading to sensitivity modifications. Another critical modulator of activation that has been studied extensively is the G-protein-coupled receptor kinases (GRK) in tandem with β-arrestins. After activation of D_2-receptors, GRKs may be recruited to phosphorylate the receptors. The purpose of phosphorylation is to attract β-arrestins [21]. These proteins can affect the signaling pathway threefold: firstly by blocking initial downstream effects of D_2-receptor activation; secondly by allowing for internalization of receptors from the plasma

membrane; and finally by initiating downstream G-protein-independent signaling events [27, 28]. Therefore, similar to RGS, the effects of activation may be modulated even in the presence of increased extracellular dopamine and particularly in the case of β-arrestins, the sensitivity of D_2 receptors may be directly manipulated.

Although not comprehensive, these mechanisms suggest that receptor modification and movement play a vital role in the process of supersensitivity. Indeed, research has indicated that changes in dopamine signaling can lead to an increased ratio of D_2^{high} to D_2^{low} receptor states in animal models [23]. With an increase in D_2^{high} receptors having greater affinity for dopamine binding, activation of dopamine transmission may be elicited to a greater extent compared to normal circumstances where the states of D_2-receptors are in oscillating equilibrium. Since the lifetime of D_2^{high} receptors are sub-seconds, these receptors have not been measured directly using PET. Accordingly, the involvement of an increase in D_2^{high} receptors in psychosis can only be hypothesized. However, evidence that individuals with schizophrenia are more likely to experience psychotic symptoms after using psychostimulants than individuals without schizophrenia, is at least consistent with the notion that a greater affinity for endogenous dopamine may compound the vulnerability of patients through enhanced D_2-receptor activation [29]. The reasons for that may be multifaceted, but if the dopamine signaling network is involved in any capacity, an end result may well be a biased state of D_2^{high} receptors. For example, selective knockouts of the RGS9 gene in mice striatum resulted in a 60% increase in D_2^{high} receptor states [22]. Without RGS regulation, receptors may adopt the D_2^{high} configuration for a longer period of time. This is consistent with the observation that cortical levels of RGS4 protein were reduced in the prefrontal cortex of antipsychotic-free schizophrenia post-mortem brains, while antipsychotic-medicated patients showed opposite effects [30, 31]. Moreover, abnormalities in GRK expression levels were also reported in schizophrenia postmortem brain, although contrasting results were described across the studies [32, 33].

While an alteration of affinity states is a potential manifestation of supersensitivity, another component of the supersensitivity phenomenon that can be directly measured is receptor density. From previous reports, the receptor upregulation model of dopamine supersensitivity also emerges as a rational mechanism worthy of consideration [34]. However, studies looking into this matter have not been consistent. In early positron emission tomography (PET) studies in humans, long-term treatment with antipsychotics was associated with an almost 40% increase in receptor density [35]. However, if a number of these imaging studies were averaged together, D_2-receptors in the striatum were calculated to have only elevated by 6% in patients with schizophrenia [10]. Differences in methodologies and radioligands used (*e.g.* PET with [^{11}C] raclopride vs. Single Photon Emission Computed Tomography with [(123)I] iodobenzamide) may yield variations in receptor numbers which may be concordant with some of the inconsistent results seen in both patients and animal models of psychosis [36]. While studies on animals concur that chronic exposure to antipsychotics lead to receptor upregulation, it seems that the process of upregulation is also dictated by the dosing regimen and the level of receptor occupancy [37]. Dopamine receptor density has also been quantified in post-mortem brains of subjects with schizophrenia. Although not fully consistent, various studies found upregulated radioligand binding (typically using [^{3}H] raclopride) in different striatal structures of schizophrenia brain [38, 39]. It should be noted that both PET-scan and post-mortem brain studies quantified receptor density using D_2-receptor antagonists, which do not discriminate between D_2^{high} and D_2^{low}. Nonetheless, these possible mechanisms of supersensitivity build curiosity to the question of whether or not the long-term utilization of antipsychotics is a factor in treatment resistance.

4. EVIDENCE FOR THE ESTABLISHMENT OF ANTIPSYCHOTICS INDUCED DSP

The theory that antipsychotics may induce dopamine supersensitivity is not new as earlier studies can be traced back several decades [40, 41]. In controlled experiments where some rats were pre-treated to long-term haloperidol and subsequently administered apomorphine several days after haloperidol withdrawal, the pre-treated rats showed greater behavioral supersensitivity—as measured by locomotor tasks—compared to control rats [42]. Chronic haloperidol pretreatment has also been shown to decrease dopamine release [43], whereas injections of exogenous dopamine into the nucleus accumbens of rats pretreated with haloperidol elicited hypersensitization effects suggesting that minor fluctuations in dopamine level may itself trigger increased psychomotor reactions [44]. The consistency of reverse tolerance observed in these animal behavioral models suggests that a translation to clinical relevancy is not overreaching. There is evidence that heightened positive symptoms in patients with schizophrenia can manifest after chronic antipsychotic treatments, especially after the discontinuation of the drug [45, 46]. The rapid onset of psychosis observed draws comparison to the DSP issue since withdrawal or rebound psychosis has been labeled a potential marker for supersensitivity.

The clinical manifestations of DSP in patients have generally been defined based on three major observations: the development of tolerance to antipsychotics, presence of tardive dyskinesia (TD), and the acute relapse of psychosis during or after treatment discontinuation (rebound psychosis) [13, 15]. These observations, that are present during the continuum of DSP diagnosis, all have iatrogenic origins, which have often resulted in the observation that increasing the dose of antipsychotics can temporarily alleviate these adverse effects, potentially by targeting the elevated density of D_2 receptors. Therefore, most retrospective studies on DSP use tolerance, rebound psychosis, and TD as strong predictors of a diagnosis. However, the drawback of using TD as a criterion is that it is a disorder that can persist for many years while DSP may be episodic. Instead, temporary movement disorders such as withdrawal dyskinesia may actually be seen as a more relatable criterion for dopamine supersensitivity [47]. Worth mentioning is the fact that many patients develop overt DSP without having a history of TD or rebound psychosis. These variations of DSP may have

developed latently and covertly masked by antipsychotic treatment. Upon dose reduction or discontinuation of the antipsychotic overt DSP appears [15].

Compared to the other descriptions of DSP, the presence of rebound psychosis seems to have the most evidence. Reviews on relapse rates after treatment discontinuation has shown several observations that are pertinent to the DSP debate. One is that relapse rates after treatment discontinuation is markedly increased with many studies indicating a recurrence of symptoms around 80-95% over a period of 2 years [48]. Moreover, inadequate protection against relapse with long-term antipsychotic treatment suggests that the therapeutic effects of these agents may diminish over time. Although not all cases of relapse are attributed to supersensitivity psychosis, there is growing support that DSP is likely responsible for a large portion of individuals that do relapse. A recent study conducted to establish the significance of drug induced DSP in patient outcomes, noted that 40% of recently relapsed individuals with positive symptoms (N=41) showed characteristics of DSP [49]. These patients were found to have experienced greater relapse symptoms and were more in need of residential care. All patients in this study were compliant with their medications suggesting that breakthrough symptoms do not require a discontinuation of treatment to observe DSP. This however raises a controversy, as it is well recognized that continuous treatment with antipsychotics versus intermittent or no treatment significantly reduces the risk of relapse and hospitalization in this population [50].

Even so, inadequate doses of antipsychotics during a relapse or breakthrough symptoms may actually reveal latent compensatory mechanisms that result in the increased susceptibility to dopaminergic activation. For example, there are reported cases that after the discontinuation of olanzapine, increased psychosis (*e.g.* auditory hallucinations, psychomotor hyperactivity) was noted that seemed in line with the characterization of DSP [51]. These symptoms disappeared after patients were restarted olanzapine at higher doses or were switched to another antipsychotic. Induced DSP was also hypothesized to have occurred after chronic utilization with quetiapine. In this case, researchers examined the efficacy of quetiapine monotherapy (N=23) in a 3-year open label study. Only 5 patients completed the study; however, with an 87% dose increase compared to baseline over the span of 96 weeks. Other patients who did not complete the study had dose increases of 127% suggesting that tolerance and potentially supersensitivity may have occurred during treatment [52].

The presence of dopamine supersensitivity during on-going antipsychotic treatment was also demonstrated for both haloperidol and olanzapine in animal studies [9]. In one experiment, rats were pretreated to a low (0.25 mg/kg) or high (0.75 mg/kg) dose of haloperidol through continuous infusion *via* osmotic minipump that mimicked a clinical dose profile and similar occupancy of D_2-receptors as measured in human patients. Subsequently, injections of amphetamine were given at days 2 and 12, as well as 5 days after the discontinuation of haloperidol. The psychomotor activity of the rats was measured after amphetamine injections. At day 2 of the haloperidol treatment, amphetamine-induced locomotor activity was effectively suppressed at both doses. However, at day 12, amphetamine produced the same locomotor activity for both haloperidol doses as well the control (saline injection) suggesting that chronic treatment with antipsychotics induces supersensitivity such that the antidopaminergic effects are overcome. When amphetamine was injected 5 days after haloperidol (high dose) discontinuation, it produced supersensitivity of locomotor activity reminiscent of previous withdrawal studies. Similar results were also found for olanzapine (10 mg/kg).

To add further support to these findings, conditioned avoidance response tests were conducted. The basic premise of the avoidance behavioral test is to observe how well the learning of a cue-associated footshock can be impaired by D_2- receptor blockade of the mesolimbic dopamine neurons. This model has a high predictive validity for antipsychotics such that a loss of efficacy may confer changes in the dopamine pathway. The experimental results of the conditioned avoidance test showed that impairment of learning was greatest at 6 days (*i.e.* haloperidol is effectively blocking the D_2-receptors), but diminished in action over the next 6 days [9]. Although impairment of avoidance was still visible at the end of the trial, the effect was significantly less than before. In addition to these behavioral tests, assays examining the receptor number and affinity of D_2 receptors found increases in the high affinity state of D_2-receptors for the high dose of haloperidol pretreatment. Lastly, cerebral microdialysis was used and confirmed that the decreased efficacy of antipsychotics was not due to increased endogenous release of dopamine over time [9].

Taken together, these findings demonstrate that the effectiveness of chronic administration of antipsychotics diminish during the period of receptor sensitization. While the mechanism that underlies the development of DSP cannot be directly measured using behavioral psychomotor tasks, it seems likely that postsynaptic signaling regulations of the dopamine pathways are affected by chronic antipsychotic administration. As an example, RGS and several other schizophrenia relevant genes were found to be downregulated in the presence of chronic olanzapine treatment [53].

Beyond the intrinsic regulators pushing D_2-receptors to its high or low binding affinity conformation, neuroplastic alterations of dopamine-specific downstream signaling cascades may be responsible for dopamine supersensitivity. Among the large repertoire of mechanisms potentially involved, the dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) is worth mentioning. DARPP-32 is mainly expressed in dopaminoceptive neurons, and integrates dopaminergic input in the environment of multiple receptor signals, including ionotropic (NMDA/AMPA) and meta-botropic (mGlu1/5) glutamate receptors [54, 55]. Under basal conditions, DARPP-32 is phosphorylated at Thr75 and sequestrates protein kinase A (PKA), a major effector of cAMP signaling. Only upon the appropriate stimulus, presumably involving multiple receptor activation, PKA is able to phosphorylate DARPP-32 at Thr34, which dissociates from PKA and becomes a potent inhibitor of protein phosphatase-1 (PP-1). Since PP-1 antagonizes most PKA activities (and thus cAMP signaling), the balance of DARPP-32 acts as a threshold that switches downstream

signals in dopaminoceptive postsynaptic terminals. Expression levels of DARPP-32 and its truncated variant, which lacks the PKA regulatory domain, were shown to be unbalanced in schizophrenia postmortem brains [56, 57]. Importantly, three polymorphisms in DARPP-32 gene were associated with both cognitive performance and expression of truncated DARPP-32 variant in schizophrenia key brain regions [57]. Moreover, phosphorylation status of DARPP-32 is influenced by virtually all psychoactive drugs that alter extracellular dopamine levels, which includes (but not limits to) antipsychotics, amphetamine, cocaine, and cannabinoids [55]. Both, typical and atypical antipsychotics were able to displace DARPP-32 balance towards the Thr34 phosphorylated form in mouse brain, favoring cAMP-PKA signals [58]. Under this circumstance, the signal intensity required for dopamine to trigger D_1-receptor downstream signals is considerably less than in a normal situation (*i.e.* the threshold is dropped), potentially acquiring supersensitivity to dopamine. These observations suggest that DARPP-32 may represent a key molecule in DSP.

Similarly, chronic haloperidol treatment in human neuroblastoma cell lines have shown that extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathways of the D_2-receptor cascade may be activated [59]. Stimulation of D_2-receptors in normal levels decreases the ERK/MAPK pathway in the striatum, which seems to be involved in the integration of neurotransmitter networks. Thus, with reduced D_2-receptor activation, ERK/MAPK pathway activation is increased. According to their experiment, increased ERK signaling ultimately led to D_2-receptor upregulation as measured by elevated receptor mRNA levels, which may be a potential DSP marker. Research on supersensitivity has started to focus more on genetic changes in patients characterized as having DSP. In a recent clinical study, a genetic distribution analysis of 5 single nucleotide polymorphisms (SNPs) of GRK6 and 3 SNPs of β-arrestin was conducted using DSP patients (selected based on previously discussed criteria) and non-DSP schizophrenia patients [60]. Although GRK6 and β-arrestins have been hypothesized to be involved in iatrogenic DSP, their results showed that there were no significant differences in the allelic and genotyping distributions of SNPs between DSP and non-DSP patients. It should be noted that the study design could have been a major limitation since the variance of the GRK6 and β-arrestin proteins may itself be a consequence of antipsychotic use. Moreover, the selection process for DSP relied on the experimenter's judgment based on prior diagnoses. With this in mind, it is also possible that other downstream D_2-receptor interacting molecules such as AKT (protein kinase v-akt murine thymoma viral oncogene homolog) or GSK-3 (glycogen synthase kinase -3) play a greater role in the differentiation of DSP [61]. Further research on dopamine pathways is needed to elucidate the biological mechanism of receptor trafficking and modifications seen in antipsychotic-induced DSP.

5. CONNECTION BETWEEN ANTIPSYCHOTIC INDUCED DSP AND TREATMENT RESISTANT SCHIZOPHRENIA (TRS)

Many patients fail to show adequate response to successive antipsychotic treatment (usually with progressively increasing dosages) resulting in a diagnosis of TRS. Among those diagnosed with TRS, a subpopulation fail to respond to both typical and atypical antipsychotics including clozapine, an antipsychotic reserved for last resort [62]. Reasons regarding the cause of treatment resistance remain elusive since symptom dimensions vary on a case-by-case basis, but most explanations have focused on the neurodegenerative and developmental aspect of schizophrenia. It has been reported that nearly half of schizophrenia patients will become treatment refractory [63]. However, it is noteworthy to consider the similar overlap between the symptomology of TRS and the characteristics of DSP, specifically the appearance of drug tolerance.

Previous clinical studies clarifying the role of DSP in TRS have estimated that more than half of TRS cases were the result of antipsychotic induced DSP [45]. A recent study found that approximately 72% of TRS patients of Japanese ancestry had symptoms of iatrogenic DSP [13]. The study involved 147 patients diagnosed as TRS as defined by the Broadest Eligibility Criteria [64]. The occurrence of DSP was based on previously published criteria of at least one episode of rebound psychosis, drug tolerance, or TD. Other symptom measurements were also evaluated using multiple clinical rating scales that included the following: Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning (GAF), Clinical Global Impression-Severity (CGI-S), and Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS). Frequency statistics revealed that 60% of patients characterized as 'DSP' had an episode of drug tolerance while approximately 45% had rebound psychosis and TD. In terms of general clinical scores, there were no correlations between TRS patients with DSP and TRS patients without DSP, but the investigators did mention that the DSP patients had marginally higher DIEPSS scores than the non-DSP patients, which might indicate an increased sensitivity to antipsychotic-induced side-effects.

The similarity in severity of symptoms between DSP and non-DSP patients with TRS undermines the confidence that differences in symptoms may allow for a clearer picture of DSP. Although the Japanese study mentioned above may have been a thorough analysis of patient history [13], the classification of either DSP or TRS is a difficult process with many uncertainties regarding the veracity of diagnoses [65]. The methodologies employed should not be considered a weak point, since the study did not include patients under treatment with clozapine. In fact, a recent analysis from the same authors found that even with patient parameters statistically matched for age, sex, family history, illness duration, and dosage at first episode psychosis to name a few, DSP sub-episodes were more prevalent in TRS group than the non-DSP group [66]. However, these types of retrospective studies have been limited to Japan, a nation that may harbor different clinical population profiles than Western countries. Therefore, the occurrence of DSP in TRS patients and non-TRS patients may vary if similar retrospective studies are conducted elsewhere. As such, interpretation of these studies should be taken with that in mind. Despite the shortcomings, the high frequency of DSP in TRS along with an overlapping characteristic of antipsychotic tolerance gives some credence of the involvement of DSP in TRS. As a side,

antipsychotic tolerance can be differentiated from treatment resistance in that there is: 1) a history of good response to antipsychotic(s), particularly in the early stage of the illness, and 2) reduced response to an antipsychotic(s) that has previously been effective, especially following rebound psychosis.

6. ROLE OF ANTIPSYCHOTICS IN PREVENTION OF DSP

Second-generation antipsychotics are often the preferred treatment for first-episode schizophrenia [67]. However, with studies showing that antipsychotic treatment may contribute to drug tolerance, and the emergence of supersensitivity psychosis, it may be necessary to explore alternative pathways of treatments. First and second generation antipsychotics, both work by blocking D_2-receptors and are very effective during early treatment periods [68]. The core of the iatrogenic DSP issue lies in long-term antipsychotic treatment where prolonged blockade of D_2-receptors has been shown to induce both upregulation and conversion to high affinity states. Thus, it may be possible to find treatments that directly target and normalize antipsychotic induced compensatory actions of dopamine signaling. One solution may be the usage of D_2-receptor partial agonists [69, 70].

The evidence for this suggestion comes from several lines of research. In animal studies, chronic treatment of direct dopamine agonists for D_2-receptors such as quinpirole decreased stereotyped behavior attributed to increased catecholamine levels in the prefrontal cortex [71]. Indeed, quinpirole can by itself cause stereotypy, but paradoxically, chronic use seems to decrease the density of D_2-receptors. Therefore, the suggestion that D_2-receptor partial agonists may potentially treat supersensitivity has merit as it may work to maintain an adequate, stable level of neurotransmission. An example of a D_2-receptor partial agonist that has been used to explore the prevention of DSP is aripiprazole [72]. Because of its unique mechanism of action, suggestions that aripiprazole may reduce DSP have been promoted [11, 72]. Specifically, aripiprazole may alleviate psychotic symptoms, prevent or stabilize relapses and show greater remission rates by acting as the hypothesized 'dopamine stabilizer'. To this end, it has been proposed that aripiprazole acts as a net antagonist when dopamine levels are high and as a net agonist when dopamine levels are low. Furthermore, aripiprazole has a unique functional profile for the modulation of G proteins where it acts as a partial agonist for $G\alpha i/o$ and an antagonist for $G\beta\gamma$ signaling [73].

With these hypotheses that aripiprazole may moderate postsynaptic receptors to prevent DSP, several studies have been undertaken to explore this supposition. Behavioral studies have been conducted to examine if chronic treatment of aripiprazole induces dopamine supersensitivity and to assess whether or not aripiprazole treated rats may reduce DSP induced by haloperidol [72]. In these experiments, rats pretreated with aripiprazole (1.5 mg/kg) did not show methamphetamine-induced locomotor hyperactivity as compared to rats pretreated with haloperidol (0.75 mg/kg). Radioligand assays using standard [^{3}H] raclopride also did not detect a striatal D_2-receptor upregulation for the aripiprazole pretreatment group of rats. On the other hand, haloperidol treatment increased receptor density by 153% compared to the control and by 126% compared to the aripiprazole group. Furthermore, switching from haloperidol (0.75 mg/kg) to aripiprazole did not produce as distinctive increase in total locomotor activities compared to switching to saline or continuing with the haloperidol treatment. Studies on binding affinity of partial agonists have also found that compared to haloperidol's capacity to elevate the high-affinity state of dopamine D_2-receptors by almost 3 fold, the treatment of aripiprazole as well as bifeprunox only elevated the D_2^{high} state to 108% and 129% respectively (as measured by the dopamine/[^{3}H]domperidone competition method) [74]. Although receptor states were modified somewhat with partial agonists, it is possible that the 1 fold increase in the D_2^{high} state will not promote the onset of DSP but may actually delay the process.

Not all current studies agree. According to a comparable experiment, chronic administration of aripiprazole for 10 days in young rats (starting at postnatal 10 days) facilitated a quantification of stereotyped behaviors [75]. The investigators noted that this effect may be due to an upregulation of D_2-receptors in the striatum, a likely manifestation of supersensitivity phenomenon. However, receptor densities are also under the influence of maturational processes. Thus, an increase in neuromotor activity cannot be solely pinpointed to repeated drug exposure since dopaminergic receptor expression tends to proliferate from birth [76].

While it can be demonstrated that chronic administration of partial agonists may not necessarily induce receptor upregulation in adult rat studies, there is a paucity of information in the clinical setting, especially in relation to patients characterized with DSP and TRS. Most studies looking at DSP in patients are observational and retrospective in nature [19, 77]. With no studies investigating the use of D_2-receptor partial agonists on patients that were later characterized as having DSP, it may be useful to examine the general trends of D_2-receptor partial agonists to see if further studies are warranted. In a randomized, double-blind, placebo-controlled study, the time to all cause discontinuation (a proxy for acceptability taking into account efficacy and tolerability) was significantly delayed for aripiprazole compared to placebo (92 vs. 60 days respectively). Furthermore, aripiprazole significantly reduced both PANSS and CGI-S scores [78]. However, the evidence that aripiprazole is more efficacious than other antipsychotics is lacking [79]. In a comparative study looking at treatment continuation of various atypical antipsychotics, aripiprazole seemed to have lower rates of relapse; however, the study design was a large observational study, which carries a lower level of evidence and provides less convincing support [80]. In a meta-analysis of comparative trials, the overall effectiveness of aripiprazole in treating psychotic symptoms was no different than olanzapine, with similar discontinuation rates compared to all groups, although the quality of data analyzed was viewed as generally poor as many studies lacked detailed methods of randomization and blinding [81]. Lastly, a recent retrospective study found that switching from a previous antipsychotic to aripiprazole as a result of DSP might actually increase relapse and exacerbate positive symptoms

[19]. This result is not a surprise given the partial agonistic nature of the drug. An explanation proposed was that as the tapering of previous the antipsychotic occurred, the extent of aripiprazole's binding to D_2-receptors increases thereby resulting in an increase in dopaminergic effects due to its intrinsic agonistic activity. Since patients with DSP may have a higher density of postsynaptic receptors, aripiprazole may induce acute relapses of psychosis. Similarly, there are many published cases where switching to aripiprazole has caused acute exacerbation of psychotic symptoms [82]. In a recent position paper investigating the best way for switching to aripiprazole, a panel of psychiatrists proposed that the overlap phase between the previous antipsychotic and aripiprazole should be more prolonged than what is currently in place. This was hypothesized to reduce the possibility of rebound psychosis caused by dopamine supersensitivity [83].

7. CONCLUSION AND POTENTIAL FUTURE STUDIES

The primary findings of the present review expose several observations. One is that the idea of iatrogenic DSP as a mechanism that may drive the onset of relapse and induce the occurrence of once previously ameliorated psychotic symptoms has support. As a controversial topic, this notion has been drawing critical attention lately with suggestions that iatrogenic DSP may also be related to TRS. Although the direct mechanism of action is currently unknown, chronic antipsychotic usage does seem to be correlated with changes in the dopaminergic signaling pathway, targeting key regulatory proteins [84, 85]. Whether alterations to the expression of these dopaminergic elements (*e.g.* GRKs, β-arrestins, ERKs) are the exact biological mechanism of DSP remain to be further examined, but measurable effects associated with DSP such as an upregulation of high affinity receptors have been linked to antipsychotics [23]. Even though many preclinical studies support the notion of antipsychotic induced DSP, there is a huge gap in the literature in terms of replicating or observing this phenomenon in human patients. A problem may lie in the characterization of DSP, as there is still a debate as to what criteria should be included. Some studies require only experiencing one of possibly 3 or 4 criteria of DSP to be diagnosed as having DSP leading to a possible overestimation of DSP cases in schizophrenia patients [77].

To build upon recent findings, future studies need to re-examine the characteristics of DSP to observe differences between the percentage of DSP patients that fulfill the criteria of rebound psychosis and drug tolerance to DSP patients that are experiencing TD. A re-estimation of these numbers may also be useful in the comparison of DSP incidence rates in response to individual antipsychotics. Furthermore, most of the studies examining antipsychotic-induced DSP have used haloperidol. It may be worthwhile to conduct comparison studies looking at how different antipsychotics compare with each other in the diagnosis and prevention of supersensitivity psychosis and its related disorders (*i.e.* TD and TRS).

The field of research in terms of examining possible treatments for DSP induced TRS, is also vacant. Iyo *et al.*, have hypothesized that there is an optimal range of D_2-receptors occupancy by antipsychotics for the treatment of DSP [11]. Their study results predict that antipsychotics with longer elimination half-lives (*e.g.*, long-acting injectables) dosed appropriately may be of benefit to patients with DSP. Currently, the only study on this issue has examined the potential of a long-acting injectable (*i.e.*, risperidone) in treating patients with TRS and DSP [77]. Results showed that both positive and negative symptom scores improved significantly for the DSP group (33.3% and 31.7% respectively) over a period of one year compared to the non-DSP group (16.7% and 16.6% respectively). They hypothesized that the sustained release of risperidone produces less peak to trough fluctuations of drug plasma levels thus providing a stable occupancy of D_2-receptors and an overall receptor stabilization effect. However, additional randomized, controlled studies are required to produce a more telling argument.

In terms of DSP prevention, partial D_2-receptor agonists such as aripiprazole may also have a 'stabilizer' effect on receptor regulation. Despite its potential, clinical cases has highlighted that switching to aripiprazole with a history of DSP symptomology may instead elicit DSP. Although this idea is purely theoretical, aripiprazole may be best suited as a first line treatment in the prevention of DSP since it may actually impede receptor changes as a result of its normalization effects. However, the connection between aripiprazole and DSP prevention is only a hypothesis, as there is no study currently examining this issue. Since aripiprazole has been on the market for almost 10 years, it may be interesting to look back at the records of patients who initially started aripiprazole treatment and measure the duration of remission and the onset of relapse to see how long DSP may have been prevented compared to other antipsychotics.

In conclusion, the story of long-term antipsychotic treatment and dopamine supersensitivity psychosis needs further support. Although preclinical experimentation has shown that the presence of supersensitivity of postsynaptic striatal D_2-receptors can be induced by long-term drug treatment, the evidence has not been wholly convincing when explored in a clinical setting. Part of the reason has been the difficulty in setting up experiments where confounding factors are controlled. A challenge has been trying to separate clinical response from the natural progression of the disorder. At present, there is an insufficiency in the literature on this topic, and more studies will need to be conducted in the near future.

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