



Tardive Dyskinesia and the Clinical Concept of Dopamine Super Sensitivity Psychosis in a Patient with Schizoaffective Disorder after Withdrawal of an Atypical Antipsychotic Drug

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Abstract

Antipsychotics are the first-line treatment for psychotic disorders, which have antagonistic effects on the D₂ dopamine-receptor, reducing dopamine mediated transmission. Long-term use of antipsychotics can potentially lead to a likely irreversible disorder called tardive dyskinesia (TD). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) defines tardive dyskinesia as a medication-induced movement disorder that persists despite discontinuation or change of the medications. While it is typical to see the development of TD with long-term use of antipsychotics, there are few reported cases reports of the development of TD with the withdrawal of antipsychotics. The development of TD symptoms with withdrawal of antipsychotics leads to the discussion of a phenomenon known as super sensitivity psychosis (SP). Super sensitivity psychosis was first defined as the emergence of psychotic symptoms with TD following the discontinuation of certain medications, typically antipsychotics. The following article presents the case of a patient diagnosed with schizoaffective disorder who developed TD after withdrawal of long standing administration of a second-generation antipsychotic, risperidone, whose symptoms began to improve after introduction and increased titration of clozapine.

Furthermore, the following article summarizes the literature on super sensitivity psychosis in patients who were discontinued on antipsychotics and current practices for the treatment of SP.

Keywords: Addiction Research; Addiction Therapy; Addiction; Antipsychotics; Dopamine

Introduction

Antipsychotics are the first-line treatment for psychotic disorders, which have antagonistic effects on the D₂ dopamine-receptor, reducing dopamine mediated transmission. Over time, however, the antagonistic effects of antipsychotics can lead to an upregulation of the D₂ receptors to produce receptor super sensitivity in the striatum. The enhanced affinity of dopamine for its receptors is thought to contribute to the phenomenon of dopamine super sensitivity psychosis (SP). In patients with schizophrenia and other psychotic disorders, these neuroadaptations could lead to a compromise in treatment efficacy, promote a relapse to psychosis, and trigger movement disorders, such as tardive dyskinesia. These effects have been seen in patients treated with either first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs), with a prevalence of 30% in schizophrenia and 70% in treatment resistant schizophrenia in patients treated with SGAs [1]. The following case report presents a patient with a diagnosis of schizoaffective disorder who develops super sensitivity psychosis symptoms after changes in her antipsychotic regimen and summarizes the literature on management for SP.

Case Description

We present the case of a 60 year-old female with a medical history of generalized anxiety disorder, schizoaffective disorder – bipolar type, hypertension, hyperlipidemia, chronic kidney disease and congestive heart failure who was admitted under involuntary status for delusions and psychosis that began a few days prior to admission. Collateral information obtained from the patient's husband revealed that the patient had been "manic" as demonstrated by a decreased need for sleep. He also states that the patient seemed to be mentally decompensating as demonstrated by displaying disorganized behaviors and speech including finding the patient standing on a stool in the closet staring at the ceiling and trying to turn on a television using a keychain. He

reported the patient also had delusions that the world is ending, that she died and is currently in heaven, and that everyone around her is deceased. He also denied any suicidal ideation (SI) or attempts that they had observed. The patient's husband also reported her mentation became acutely worse over the past few days, which prompted her presentation to care. This was demonstrated by disorientation to the day and time, repeatedly asking the same questions, and forgetting her doctor's names, whom she is usually able to identify. The patient is a poor historian as demonstrated by stating she is unsure why she is in the hospital, but believes she was admitted because of a stomach ache. She did however endorse a depressed mood, poor sleep, poor appetite, low energy, and poor concentration; she denied any guilt.

Collateral information was obtained regarding the patient's psychiatric history up to the point of this admission. The patient's husband reported four months prior to this admission, the patient was expressing delusional thoughts and had auditory hallucinations. This behavior prompted admission to a behavioral health facility. While in treatment, the patient became catatonic and was transferred to a different behavioral health facility where she received eleven electroconvulsive therapy (ECT) treatments. He further stated that the patient was no longer catatonic after receiving ECT and was stable to

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be discharged home where the patient continued to receive ECT as an outpatient. He stated that the patient had been in her normal state of mental and physical health until development of her current symptoms a few days before this admission.

On mental status examination, the patient was calm on approach. Patient stated her mood is "fair and tired" and her affect was depressed and blunted. She was not oriented to place, time, or situation, but was oriented to self. She denied current suicidal or homicidal ideation. Her attitude was cooperative, calm, but unengaged as demonstrated by decreased eye contact and disinterest in conversation. There was no psychomotor agitation observed at that time. Speech was minimally coherent with one worded answers and low volume. Her thought process was slow and impoverished as demonstrated by increased latency of speech and looseness of association. She denied auditory, tactile, and visual hallucination to the best of her ability. She displayed overt delusions as demonstrated by stating she thought she was dead and everyone surrounding her was an angel. Memory was impaired as demonstrated by not being able to recall the events surrounding her hospital admission.

The patient's psychiatric medications included trazodone 50 mg at bedtime (QHS), clonazepam 0.25 mg twice daily (BID), and risperidone 2 mg BID. The patient's husband confirmed these medications and stated she had been taking them regularly for many years as prescribed. The patient's course was complicated by progressively worsening psychosis. She became acutely agitated with disorganized behavior demonstrated by screaming in common rooms, walking around her room naked, and urinating and defecating in her bed. The internal medicine team was consulted to potentially rule out causes secondary to nonpsychotic origin. The medicine team evaluated the patient and determined her behavior and decompensating mental status was not due to any medical causes; complete blood count, comprehensive metabolic panel, and urinalysis showed no abnormalities. Neurology was also consulted and had no recommendations for changes in current management. The decision was made to begin clozapine 12.5 mg QHS for treatment resistant psychosis. After five days of administering clozapine, the patient continued to demonstrate disorganized behavior as displayed by yelling in common rooms and expressing delusions. The decision was made to taper risperidone over the next ten days and immediately increase clozapine to 25 mg QHS for treatment resistant psychosis.

The patient's hospital stay was further complicated by extrapyramidal symptoms (EPS) witnessed by the nursing staff. Upon evaluation of the patient, she appeared to have symptoms consistent with tardive dyskinesia (TD) as demonstrated by abnormal movements of the mouth and jaw with lip smacking. It was noted by the patient's nurse that these symptoms were not present at initial admission, but now seen for the first time. Patient also did not appear restless nor with other symptoms that would otherwise suggest akathisia at the time of exam. Tardive dyskinesia is made worse with benztropine (Cogentin) and Benadryl/ antihistamines, and is typically treated with valbenazine or tetrabenazine, neither of which are available at the facility the patient is currently admitted to. Of note, risperidone was recently tapered over the past ten days with the final dose being the morning of TD symptom onset. Clozapine is less likely to cause tardive dyskinesia when compared to other antipsychotics. As such, the plan was to continue with current medications, avoiding benztropine (Cogentin) and benadryl / antihistamines, and re-evaluate the patient for ongoing treatment decisions. The patient was subsequently examined the next day, physical examination showed signs and symptoms of TD

including irregular movement of mouth / tongue and an irregular blink. Clozapine 25 mg was increased to BID. The patient subsequently began to show improvement in signs and symptoms of TD six days after the increase of clozapine including less irregular movements of the mouth and tongue. There was no dystonia, akathisia, or EPS tremor. The patient's TD symptoms continued to improve by evidence of less lip smacking and less irregular blinking until she was discharged with close outpatient follow up.

Discussion

Antipsychotics are the first-line treatment for psychotic disorders, which have antagonistic effects on the D₂ dopamine-receptor, reducing dopamine mediated transmission. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) defines tardive dyskinesia as a medication-induced movement disorder that persists despite discontinuation or change of the medications [1]. The disordered movements seen in tardive dyskinesia (TD) are thought to be caused by the blockade of D₂ dopamine-receptors. The movement disorders include akathisia, dystonia, buccolingual stereotypy, chorea, tics, and other abnormal involuntary movements of the face, mouth, jaw, and extremities [2]. Most often, these dyskinetic disorders precipitate following chronic antipsychotic administration, however, there are reported cases of patients developing symptoms consistent with TD after withdrawal of antipsychotic medications[3].

Super sensitivity psychosis (SP) was first defined as the emergence of psychotic symptoms with tardive dyskinesia and a decrease in prolactin levels following the discontinuation of certain medications. In the context of antipsychotics, there are four main clinical characteristics used to define medication-induced SP, including: 1) rapid relapse of symptoms following the discontinuation, dosing change, or a change in antipsychotic medication; 2) new onset tolerance after previously having therapeutic effects; 3) presence of TD; and 4) psychotic exacerbations due to life stressors. Additionally, in order to diagnose SP, a patient must also have been taking an antipsychotic for 3 months. It is hypothesized that what was previously described as "treatment resistant schizophrenia" is in fact SP, with SP being observed in 70% of treatment-resistant schizophrenic patients versus 30% in non-treatment resistant patients [4].

Second-generation antipsychotics (SGAs) are widely used to treat a variety of psychotic symptoms, having largely replaced first-generation antipsychotics (FGAs) due to their more favorable side effect profile. Psychosis is believed to be due to excess dopamine signaling in the striatum, therefore both FGA and SGA work by blocking dopamine transmission in the striatum via the dopamine D₂ receptors [5]. The D₂ receptor is important with its involvement in SP, as antipsychotics are antagonists of this receptor postsynaptically [6]. It has been shown that the D₂ receptor is prone to plasticity and remodeling. The effect of prolonged antipsychotic use on the intracellular system leads to an increased number of postsynaptic D₂ receptors within the striatum, leading to hypersensitivity over time[4]. Our patient had been receiving chronic antipsychotic treatment for schizoaffective disorder for several years prior to her admission to the hospital. Therefore, it can be postulated that at this time she would have had an increased density of dopamine receptors in her striatum, which would have put her at increased risk for SP. Shortly after a change to her medications, she developed TD symptoms such as lip-smacking, which was not experienced previously. This illustrates the possibility that our patient was experiencing SP due to prolonged use of her antipsychotics, which led to negative symptom development when her medications were

adjusted. As studies have demonstrated previously, as patients continue to take antipsychotics, the density of these receptors increase causing the need for increased levels of antipsychotics in order to control the increased dopamine levels to maintain symptom control[7]. This further perpetuates tolerance and increases the risk for SP [4].

Similar to our case, another case report described a female patient who experienced TD after being abruptly withdrawn from risperidone, with resolution of symptoms occurring after starting a new antipsychotic medication. While TD can occur in all ages, it has been shown to be most common in elderly patients, particularly elderly female patients[8]. The patient we presented in this case was an elderly female, and given the previous findings of high-risk of TD and SP in this age group, greater care and monitoring should be taken when adjusting antipsychotic medications.

Due to the risk of severe psychosis and TD, it has been proposed that intermittent dosing, use of long-acting antipsychotics, and controlled tapering can help prevent SP. Furthermore, it is widely accepted that SGAs are less likely to invoke super sensitivity and drug-induced movement disorders when compared to FGAs, and therefore are the preferred first choice of medication when treating psychosis[4]. With this being said, many studies suggest the use of long-acting injectables, such as risperidone to prevent and reduce the incidence of SP.[4,9] A 12-month study evaluating treatment resistant patients (TRP) and dopamine super sensitivity patients (DSP) found that DSP had a significant improvement of symptoms while on long-acting risperidone, when compared to TRP. DSP patients at baseline had more severe extrapyramidal symptoms, however they had a 62% higher response rate to long-acting risperidone compared to 21% of non-DSP patients [9]. The long-acting and high-potency injectables have shown to stabilize the receptors and minimize fluctuations of dopamine, thereby decreasing the incidence of SP [4].

When considering treatment for the symptoms of SP, medications should aim to reduce the increase in D₂ receptor density. One study suggests the use of anti-seizure medications such as valproate, carbamazepine, or phenytoin. The early addition of these medications with an antipsychotic has shown to potentiate the effects of the antipsychotic, thereby reducing the need for increased doses, and decreasing the likelihood of the patient developing SP.[10] Electroconvulsive (ECT) therapy has also illustrated the ability to normalize the density of D₂ receptors, which was also found with our patient who had resolution of her catatonia after eleven ECT treatments [4].

Another possible treatment option is the use of clozapine for SP symptoms. A study of 15 patients experiencing SP symptoms found that 13 of the 15 patients experienced no further SP symptoms after the initiation of clozapine for the duration of the 2.65 year follow-up [11]. The efficacy of clozapine on SP symptoms has been thought to be due to its role on GABAergic neurons and its potency on D2 receptors, however, this has not been clearly defined. Initially, our patient had no symptom relief upon starting Clozapine 25 mg once daily, but upon increasing the dose to twice daily dosing and tapering down off risperidone, her TD symptoms improved within six days. While our patient did not have complete resolution of her TD symptoms, she did experience symptomatic improvement. It is shown that only 33% of patients will have complete resolution of TD symptoms within two years, so it was not expected for her to have had complete resolution of the symptoms during our time frame of care for her [3].

Conclusion

This case report highlights the importance of close medication follow-up and management with patients on long-term antipsychotics. The abrupt cessation or change of such medications can have deleterious consequences, with the most dangerous being tardive dyskinesia (TD). Therefore, it is important when considering medical management for patients with antipsychotics that consideration be placed into long-term injectables, such as risperidone, along with use of a second generation antipsychotics over first generation antipsychotics in order to prevent TD and super sensitivity psychosis (SP) from occurring. This is especially important in patients who need long-term management with antipsychotics. In addition, if a patient needs to be switched to another antipsychotic, slow tapering and close management is important in order to quickly identify TD symptoms and prevent the occurrence of SP. Finally, SP should be considered in patients who appear to be treatment resistant, as increasing doses of antipsychotics in this case can have continued damaging effects due to tolerance and hypersensitivity to the medications.

The use of antipsychotics has been demonstrated to cause super sensitivity psychosis, with the most extreme form being tardive dyskinesia as highlighted in this case report. It is therefore important to carefully monitor patients when adjusting or tapering off any antipsychotics, especially those at higher risk, in order to prevent super sensitivity psychosis symptoms. It is recommended to use long-acting injectable, such as risperidone, as previous studies have shown it to reduce the risk of this phenomenon (Table 1).

Table 1: Long-acting injectable for antipsychotics.

Serum	Results	Reference range
White Blood Cells (x10 ⁹ /uL)	8.4	4.5 - 11.0
Hemoglobin (g/dL)	11.1	12.0 - 16.0
Mean Corpuscular Volume (fL)	88.9	80.0 - 100.0
Platelet Count (x10 ³ /uL)	218	140 - 450
Glucose (mg/dL)	92	136 - 145
Blood Urea Nitrogen (mg/dL)	31	5 - 25
Creatinine (mg/dL)	2.15	0.44 - 1.0
Sodium (mmol/L)	145	135 - 146
Potassium (mmol/L)	4.1	3.5 - 5.2
Chloride (mmol/L)	108	96 - 110
Calcium (mg/dL)	9.6	8.5 - 10.5
Magnesium (mg/dL)	2.0	1.3 - 2.5
Bicarbonate (mmol/L)	25	24 - 31
Alkaline phosphatase (U/L)	75	38 - 126
Total protein (g/L)	6.1	6.0 - 8.0
Albumin (g/dL)	3.5	3.5 - 5
Bilirubin, Total (mg/dL)	0.4	0.2 - 1.3
Aspartate aminotransferase (U/L)	14	10 - 42
Alanine aminotransferase (U/L)	17	10 - 60

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