Lybalvi (Olanzapine and Samidorphan) in the management of schizoaffective disorder in an adult with Prader-Willi syndrome.

Abstract:

Prader-Willi syndrome (PWS) is a neurodevelopmental genomic imprinting disorder characterized by obesity, behavioral issues, mental illness, and self-injury. Managing psychiatric symptoms in PWS is a clinical challenge because of significant weight gain associated with antipsychotic medications in an already obese patient population. We report a case of a patient with Prader-Willi syndrome and schizoaffective disorder, depressive type, treated with Lybalvi (olanzapine and samidorphan), leading to the resolution of hallucinations without a significant increase in weight. It might be a novel pharmacological option for treating psychiatric illness in PWS. This case focuses on the need for an individualized treatment plan and further research into the safety of antipsychotics in patients with PWS comorbid with psychiatric illnesses.

Keywords: Prader-Willi syndrome, schizoaffective disorder, olanzapine, samidorphan, case report

Introduction:

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder (Parikh et al., 2025). The incidence of Prader-Willi syndrome is 1:15,000 to 1:30,000 (Manzardo et al., 2018). Birth hypotonia is followed by hyperphagia, obesity, and abnormal behavior in children (Butler et al., 2019). Other features include developmental delay, learning problems, short stature, mild craniofacial dysmorphism, and endocrine disorders (Shelkowitz et al., 2018). PWS is either due to a lack of expression of imprinted paternal genes or when both chromosome 15s are inherited from the mother (Dyskens et al., 2003). Specific PWS genetic subtypes may be responsible for specific phenomenology of psychiatric symptoms and behavioral problems associated with the syndrome (Dykens et al., 2003).

Prader-Willi syndrome is frequently characterized by co-occurring behavioral challenges (Arron et al., 2011). Aggression, obsessive-compulsive tendencies (e.g., hoarding food and other items, demanding the same routines and repetitive actions), skin excoriation, temper tantrums, and high risk of self-injury are the most common psychiatric conditions associated with PWS (Clarke et al., 2002). Individuals with maternal uniparental disomy (mUPD) had a higher incidence of psychiatric illnesses, i.e., about 6.7 per 100 person-years with frequent episodes and recurrences (Soni et al., 2006). Psychiatric symptoms may be mood-related symptoms with or without psychotic features in all genetic subtypes of PWS (Soni et al., 2006).

Schizoaffective disorder (SAD) is a long-term psychiatric condition, often diagnosed in individuals who present with both mood-related and psychotic symptoms (Miller et al., 2019). The diagnostic criteria of SAD require the following: 1. A period of illness with a major mood episode concurrent with schizophrenia, 2. At least two weeks of delusions or hallucinations in the absence of a major mood episode during the lifetime duration of the illness, and 3. Mood symptoms that are present for the majority of the total active and residual illness duration (DSM-5 TR).

The psychotic symptoms experienced by patients with PWS are often unusual in manner and difficult to categorize into the current diagnostic classification system (Aman et al., 2018). Anxiety, movement disorders, confusion, hallucinations, persecutory delusions, sleep dysfunction, and mood swings are the most common presentations in individuals with PWS (Aman et al., 2018). Antipsychotics, lithium, and benzodiazepines have been used to treat mental disorders in PWS patients (Singh et al., 2019). SAD is a hybrid of the "schizophrenia spectrum or affective disorders" that clinicians often use to categorize the complex psychotic phenomena observed in patients with this condition (Singh et al., 2019).

Here, we present a case of a 23-year-old female, Ms. P, diagnosed with Prader-Willi syndrome and schizoaffective disorder treated with an olanzapine and samidorphan combination.

Case Presentation:

We present a 23-year-old female, Ms. P, with a history of Prader-Willi syndrome diagnosed at 14 months of age, with complaints of hearing voices unheard by others, delusions that she is in immediate danger, and fluctuating episodes of elevated and depressed moods for the past nine to ten years. Her symptoms were acute in onset and episodic in course. It was associated with a decreased need for sleep, followed by a decreased interest in her regular activities at home during the episodes. Hallucinations and delusions were present even without the mood symptoms for at least a month, and mood symptoms prevailed for the entire course of her illness. Ms. P reported no history of suicidal or homicidal ideation. On a mental status examination, Ms. P appeared older than her stated age, with physical features of PWS. She was cooperative but mildly distracted with slow speech. She described her mood as feeling sad, tearful, crying, and angry. Her affect was restricted. She heard different types of voices all the time, which were bothering her even in her sleep. She also reported obsessive and intrusive thoughts and behaviors. She felt helpless, worthless, and hopeless. Insight was poor, not acknowledging her mental illness.

Her perinatal history is significant for a risk factor: her mother's age was 43 at the time of her birth. There is no known family history of psychiatric or any other genetic conditions. Given the characteristic limitations of PWS, Ms. P's mother is her legal guardian and provides essential

support for all activities of daily living and vocational needs. During childhood and adolescent years, she presented difficulties adapting to school, displaying frequent tantrums, being oppositional and defiant, having learning difficulties, and having a significant lack of social skills and attention span. She was never diagnosed with attention deficit disorder or any other psychiatric condition, nor did she receive any treatment in her early years for any associated behavioral problems. She gives no history of substance use.

At the age of 14, she presented with an episode of "weird" behavior while she was at a school camp, where the patient reported hearing voices, not remembering who she was, and claiming that she was in danger, with agitation and aggressiveness. She was initially diagnosed with bipolar disorder at that time and hospitalized for treatment. She was treated with several medications over the years, including lamotrigine, topiramate, valproate, and lithium. Although the mood symptoms were partially controlled, symptoms such as hallucinations and delusions remained persistent.

After she presented to us, based on the history and examination, schizoaffective disorder was then suspected, and the patient was started on a trial of atypical antipsychotics, initially antipsychotics such as aripiprazole 400 mg every 30 days and risperidone 2 mg daily. With both, rapid control of positive psychotic symptoms was achieved, but weight gain and increased appetite were reported, which was unacceptable in this patient with overweight and a baseline increased appetite due to her genetic condition. Lurasidone was then tried due to its safer profile in terms of weight gain and metabolic adverse effects, but remission of positive symptoms was unsuccessful.

A trial with Lybalvi (olanzapine-samidorphan) was then begun, starting on 5-10 mg daily, which showed only mild improvement of her positive symptoms. The dose was then increased to 10-10 mg and, one month later, to 15-10 mg. By the end of the first week of treatment, she reported no hallucinations or delusions. By the second week, the patient displayed a significant improvement in her vocational functioning as well as psychotic symptoms. The parents reported that she was sleeping better without an increase in her appetite.

Discussion:

Prader-Willi Syndrome (PWS) is a severe genetic disorder (Shelkowitz et al., 2012). It is caused by the loss of paternal gene expression due to paternal gene deletion in the chromosome 15 region (q11-13), maternal uniparental disomy (UPD), or imprinting defects (Clarke et al., 1998). PWS is the most common cause of life-threatening obesity, in which the patients present with behavioral symptoms including aggression and obsessive-compulsive actions and habits (e.g., skin picking) (Singh, 2018). Genetic subtypes in PWS affect the behavioral manifestations and their severity (Dysken et al., 2003). A study showed that patients with paternal gene deletion

were more likely to demonstrate predominantly depressive symptoms without psychosis (Aman et al., 2018). In contrast, patients with mUPD presented with features of bipolar affective disorder with psychotic features (Soni et al., 2008).

Patients with PWS often have a reduced quality of life due to the associated behavioral patterns and comorbid psychiatric illnesses (Deest et al., 2022). Mental disorders associated more frequently with this condition are schizophrenia, mood disorders, and obsessive-compulsive disorders (Steinhausen et al., 2003). More than 50 percent of persons with PWS and psychiatric symptoms had a depressive disorder with psychotic features (Sinnema et al., 2011). The majority of PWS patients with psychiatric illness have atypical mood disorders with or without psychotic features, and fewer have schizophrenia spectrum disorders (Soni et al., 2008). In our case, the patient was diagnosed with "schizoaffective disorder, depressive type" with PWS, which is only reported in one other publication (Singh et al., 2019).

Psychiatric and behavioral conditions associated with PWS often lead to caregiver burden because of their symptoms and management, and there are currently no guidelines about the use of psychotropic medications in these cases (Lanfranchi et al., 2012; Soni et al., 2007). Antipsychotics (e.g., risperidone and aripiprazole), antidepressants (e.g., fluoxetine and sertraline), and mood stabilizers have been implemented in pharmaceutical treatment plans; however, there is limited research regarding the use of psychiatric medications in PWS (Araki et al., 2010; Soni et al., 2007; Bonnot et al., 2015). Only a few case reports have been documented regarding the use of antipsychotic drugs in PWS (Clarke et al., 2002; Sinnema et al., 2012). First- and second-generation antipsychotics are being prescribed, but because their safety profiles are overlooked, high rates of extrapyramidal symptoms (EPS), weight gain, and hormonal imbalances have been reported (Deest et al., 2022). The use of risperidone and olanzapine has been reported in the literature in the management of a 37-year-old woman with PWS and psychosis, which led to hypothermia (Phan et al., 1998). The use of olanzapine as monotherapy or with samidorphan in PWS has not been systematically studied yet.

Atypical antipsychotics such as olanzapine lead to weight gain, type 2 diabetes mellitus, and obesity (Lord et al., 2017). The early-onset hyperphagia in PWS causes obesity in these patients (Steinhausen et al., 2004). The presentations pose a challenge when treating PWS associated with psychiatric illnesses, such as schizoaffective disorder, as presented in our case with atypical antipsychotics. The Clinical Antipsychotic Trials of Intervention Effectiveness (CAITE) study found that olanzapine had a significant improvement in psychiatric symptoms, a longer period of effective treatment, and the lowest discontinuation rate in the management of psychotic symptoms; however, there are concerns about the association of olanzapine with weight gain and metabolic issues (Nasrallah et al., 2004). Olanzapine and samidorphan may provide an effective treatment for schizophrenia with a decreased risk of weight gain and other metabolic adverse effects (Silvermann et al., 2017).

Samidorphan is a drug that blocks opioid receptors and helps reduce weight gain (Chaudhary et al., 2019). Augmenting olanzapine with samidorphan has gained attention in the treatment of schizophrenia (Corrao et al., 2022). This helps to preserve olanzapine's antipsychotic effects and balances its metabolic side effects, especially weight gain. Several studies support the effectiveness and tolerability of this drug combination (Gao et al., 2022).

In our case, we were challenged with prescribing an effective antipsychotic medication without increasing the patient's weight. After the failure of the antipsychotic trial with lurasidone, treatment with olanzapine and samidorphan was started. Control of symptoms without a significant increase in weight was achieved with this combination.

Understanding the intrinsic limitations of this study, further clinical trials are recommended to provide reliable evidence that this intervention can help this group of patients.

Conclusion:

This case illustrates the difficulties in diagnosing and treating mental illnesses in the setting of Prader-Willi syndrome. The co-occurrence of PWS and schizoaffective disorder, depressive type, is an uncommon and rarely reported clinical entity, and the lack of treatment guidelines puts psychiatrists in a dilemma. The metabolic profile of PWS, characterized by hyperphagia and a strong predisposition toward obesity, renders the use of conventional antipsychotics particularly hazardous. In this context, the olanzapine and samidorphan combination has emerged as an effective and rational therapeutic choice, providing adequate psychotic coverage while significantly reducing the metabolic risk associated with olanzapine therapy. Our patient's positive outcome contributes to the scientific literature that supports the use of olanzapine and samidorphan in metabolically vulnerable individuals. Further studies are recommended to establish clear evidence-based recommendations for the use of psychotropic drugs in patients with PWS, with a focus on both efficacy and side effect profile.

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