JPPT | Case Report

Pitolisant in an Adolescent with Prader-Willi Syndrome

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This case report evaluates the potential benefit of pitolisant in a 15-year-old female with Prader-Willi syndrome, obsessive-compulsive disorder, autism spectrum disorder, and mild intellectual disability. Due to its action on the H3 receptor, it enhances central activity of histaminergic neurons resulting in increased alertness, irrespective of the loss of orexin neurons seen in narcolepsy. Additionally, it is thought to modulate various other neurotransmitter systems including acetylcholine, norepinephrine, and dopamine. Pitolisant has the potential to improve many symptoms in patients with Prader-Willi syndrome and it appears to be well tolerated with minimal side effects observed. Therefore, the use of pitolisant should be considered in patients with Prader-Willi syndrome who fail a psychostimulant trial.

ABBREVIATIONS ABC-C, Aberrant Behavior Checklist – Community; CNS, central nervous system; ECG, electrocardiogram; EDS, excessive daytime sleepiness; FDA, US Food and Drug Administration; PHQ-9, Patient Health Questionnaire; PWS, Prader-Willi syndrome; QTc, ECG interval from the QRS complex to the end of the T wave, corrected; SCARED-Parent, Screen for Child Anxiety Related Disorders; SSRI, selective serotonin reuptake inhibitor

KEYWORDS case report; histamine-H3 receptor antagonist; pediatric; pitolisant; Prader-Willi syndrome

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Introduction

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13, with a prevalence rate estimated between 1/10,000 and 1/30,000.[1-5] This genetic disorder is associated with a broad phenotypic and metabolic profile, which can vary greatly throughout development with food-seeking behaviors, growth-hormone insufficiency, and neuropsychiatric/behavioral issues becoming prominent in school-age years.[2,3] Key prognostic factors include the development of diabetes mellitus type 2, obstructive sleep apnea, and hypertension, among others. A distinctive behavioral phenotype including irritability and obsessive-compulsive characteristics in combination with excessive daytime sleepiness (EDS) and other disordered sleeping patterns, creates a complex clinical picture with variable response to psychotropic medications.[4-6]

Psychotropic medications have been evaluated in youth with PWS to manage behavioral disturbances, comorbid psychiatric disorders, and EDS.[6,7] The evidence supporting efficacy of these medications in PWS is weak, particularly as monotherapy.[6] As a result, individuals often are treated with several psychotropic medications in an effort to manage ongoing symptoms; however, this increases the risk for drug-associated adverse effects. Given such concerns, providers often seek novel pharmacologic therapies.

Pitolisant (Wakix, Harmony Biosciences, Plymouth Meeting, PA) is a potent histamine H3 receptor antagonist/inverse agonist that is approved in Europe for the treatment of EDS in adults with narcolepsy, with or without cataplexy.[8-13] As a result of its action on the H3 receptor, it stimulates widespread release of histamine throughout the CNS, in addition to other wake-promoting neurotransmitters (i.e., dopamine, norepinephrine, and acetylcholine) in the cerebral cortex.[9,11-15] The role of the histamine H3 receptor has been evaluated in a variety of neuropsychiatric conditions (e.g., attention-deficit/hyperactivity disorder, Tourette syndrome, Alzheimer disease, Parkinson disease) due to histamine's wide-reaching effects on maintenance of sleep, neuroendocrine function, feeding and appetite, neuronal hyperexcitability, cognition, memory, and attention.[16] Given the unique mechanism of pitolisant and its effects of histamine, norepinephrine, dopamine, and acetylcholine, pitolisant may provide a novel treatment approach for PWS. This case describes the use of pitolisant in a pediatric patient with PWS.

Case Report

A 15-year-old female (65 kg) with PWS, obsessive-compulsive disorder, autism spectrum disorder, mild intellectual disability, hypothyroidism, and scoliosis was followed by outpatient psychiatry with ongoing complaints of irritability, anxiety, aggression, rigid thinking, and EDS. She had taken a variety of psychotropic medications since she was 11 years of age with variable response, including psychostimulants, SSRIs, α-2 agonists, and atypical antipsychotics (Table 1).

Given ongoing restlessness, difficulty with transition,

Table 1. Psychotropic Medication History

Medication	Indication	Reason for Discontinuation	Maximum Dose	Duration of Treatment
Aripiprazole	Difficulty with impulse control	Increased agitation	1 mg at bedtime	9 days
Buspirone	Anxiety	Not applicable	10 mg in the morning; 5 mg in the evening; 10 mg at bedtime	Current therapy
Escitalopram	Repetitive behavior/ anxiety	Aggression	12.5 mg daily	5 yr (inconsistent)
Guanfacine	Anxiety	More tantrums and more destructive during tantrums	0.5 mg twice daily	8 mo (inconsistent)
Modafinil	Daytime sleepiness	Lack of perceived benefit; increased anxiety and aggression	100 mg daily	4 yr
N-acetylcysteine	Obsessive-compulsive behaviors; irritability; aggression	No longer needed	900 mg daily	4 yr
Oxytocin	Anxiety and social awareness/ connection	Lack of perceived benefit; simplification of medication regimen	16 units intranasal every other day	3 yr
Risperidone	Aggression	Not applicable	0.25 mg 3 times a day	Current therapy

insistence on sameness, daytime sleepiness accompanied by distractibility/irritability, and behavioral outbursts in which she would throw herself to the floor, the patient's family became interested in a trial of pitolisant, which they had heard about from other families who had trialed it in their children with PWS. At this time, her psychotropic medication regimen consisted of escitalopram 2.5 mg daily, buspirone 10 mg twice daily, risperidone 0.125 mg twice daily, and N-acetylcysteine 900 mg daily. She was also receiving growth hormone, estradiol, and levothyroxine.

After receiving pitolisant through compassionate release and discussion with the outpatient psychiatrist/psychiatric pharmacist, the patient was started on pitolisant 4.5 mg daily. Prior to initiation, an ECG was recommended by the pharmacist and drug-interaction evaluation was performed.

Within 10 days of starting pitolisant, the patient's mother noted that her daughter could more easily complete academic tasks and required less assistance completing tasks at home, something she had not been able to do for years. She continued to perseverate on specific actions of others (e.g., clothes they wear, food they eat) and to be rigid (e.g., insistence on sameness) in her interaction with others, but was noted to have less associated behavioral outbursts. No other changes to her psychotropic medication were made in an effort to monitor the improvement of ongoing symptoms following initiation of pitolisant.

Two months later, the dose of pitolisant was increased to 9 mg daily, but symptoms persisted. Shortly after the dose was increased, it was noted that the patient had improved muscle tone, was walking more quickly with less hyperflexibility, had reductions in daytime sleepiness, was more alert and engaged with others, and had fewer behavioral outbursts and aggression. Although she appeared to have a greater ability to focus on cognitive tasks, she continued to struggle with completing schoolwork and responding to questions. She maintained a very rigid thought process and a fixed routine (e.g., continuing to wear winter clothes, despite warm weather in winter months).

At this point, 3 rating scales were introduced to aid in assessing the patient's progress on pitolisant. The Patient Health Questionnaire (PHQ-9) modified for teens[17] and Screen for Child Anxiety Related Disorders (SCARED)-Parent[18] were used to assess ongoing depressive and anxiety symptoms. Additionally, the Aberrant Behavior Checklist – Community (ABC-C)[19] was used to evaluate irritability and lethargy. The patient was evaluated at 2 and 12 months, and the scores for these 3 rating scales are reported in Table 2. These rating scales had not been used previously in the patient given complexity of symptom presentation.

Three months later, the dose of pitolisant was increased to 18 mg daily in an effort to improve ongoing rigidity and insistence on sameness. Following this increase, the parents reported that she was better able to reason through situations. For example, although she continued to have behavioral outbursts at home and school, she was noted to have improved frustration tolerance. Her mother identified this as a significant improvement that she attributed to pitolisant. Even her school noticed that she was easier to redirect when upset and that she would get upset less frequently.

While family and teachers at school continued to notice improvement, the dose of pitolisant was increased to 27 mg and eventually to 36 mg daily. During this time, the dose of escitalopram was slowly tapered and discontinued, N-acetylcysteine was also discontinued, and the buspirone dose was slowly decreased under the direction of her psychiatrist. Following these changes, parents noticed less aggressive behaviors, less rigid thinking, improved sleep, and increased attention and focus at home and at school. It has been noted through behavioral charts and data that her behavior at school has improved immensely. Although it is difficult for parents to identify whether these positive changes are attributed to pitolisant, other medication changes, or her ongoing development, they report an overall satisfaction with pitolisant. However, parents continue to report underlying anxiety, particularly for 2 to 3 days following a pitolisant dose increase. Her current medication regimen consists of buspirone 5 mg twice daily, risperidone 0.125 mg twice daily, and pitolisant 36 mg daily, in addition to estradiol, growth hormone, and levothyroxine daily.

Clinical rating scales were repeated 12 months post–pitolisant initiation and were noted to significantly improve in specific domains, most notably, in terms of depression, irritability, lethargy, and hyperactivity (Table 2, Rating Scales). She improved in 2 of the 3 scales, PHQ-9: Modified for Teens and the ABC-C; however, her SCARED-Parent score increased due to worsening in the following categories: panic disorder, separation anxiety, and most notably, generalized anxiety.

Since initiation of pitolisant, the patient's mother reported some potential adverse effects. The patient was noted to have increased sweating, salivation, and drooling; however, these adverse effects did not seem to get worse with increasing dosage of pitolisant. Although there was concern that she may have gained weight after pitolisant initiation, her body mass index chart only increased 2% in the 12 months while she was on pitolisant. Furthermore, it is difficult to determine if this increase is associated with the medication or was due to other natural factors, like puberty

Discussion

Prader-Willi syndrome is a complex genetic disorder caused by the lack of expression of genes on

Table 2. Three Rating Scales Used to Assess the Patient's Progress on Pitolisant

Rating Scale	2-mo Assessment Period	12-mo Assessment Period
PHQ-9: Modified for Teens*	Score = 12 (moderate depression)	Score = 8 (mild depression)
SCARED-Parent†	Total score = 8 Panic disorder (score = 1) Generalized anxiety (score = 3) Separation anxiety (score = 1) Social anxiety (score = 3) Significant school avoidance (score = 0)	Total score = 13 Panic disorder (score = 2) Generalized anxiety (score = 6) Separation anxiety (score = 2) Social anxiety (score = 3) Significant school avoidance (score = 0)
ABC-C‡	Irritability (score = 15; max score = 45) Lethargy (score = 21; max score = 48) Stereotypy (score = 8; max score = 21) Hyperactivity (score = 23; max score = 48) Inappropriate speech (score = 6; max score = 12)	Irritability (score = 10; max score = 45) Lethargy (score = 17; max score = 48) Stereotypy (score = 10; max score = 21) Hyperactivity (score = 19; max score = 48) Inappropriate speech (score = 6; max score = 12)

ABC-C, Aberrant Behavior Checklist – Community; max, maximum; PHQ-9, Patient Health Questionnaire; SCARED-Parent, Screen for Child Anxiety Related

* A score of 0–4 = minimal depression, 5–9 = mild depression, 10–14 = moderate depression, 15–19 = moderately severe depression, 20–27 = severe depression. Scores < 4 may not need treatment. Scores 5–14, treatment is per the clinical judgement of the physician based on the patient's functional impairment and duration of symptoms. Scores > 15 warrant treatment using an antidepressant, psychotherapy, and/or a combination of treatment.

† A total score of ≥25 may indicate a presence of an anxiety disorder. Scores > 30 are more specific. A score of 7 for specified items may indicate panic disorder or significant somatic symptoms. A score of 9 for specified items may indicate generalized anxiety disorder. A score of 5 for specified items may indicate separation anxiety disorder. A score of 8 for specified items may indicate social anxiety disorder. A score of 3 of specified items may indicate significant school avoidance.

‡ ABC-C is a validated tool for caregivers to assess behavioral and emotional difficulties in youth with autism spectrum disorder and/or intellectual disabilities. It contains questions categorized into 5 specific symptom domains and uses a 0 to 3 Likert scale for scoring each question. Scores are evaluated based on mean change over time.

the paternally inherited chromosome 15q11.2-q13 region. Throughout development, the characteristic phenotype of this syndrome varies. Infancy is typically characterized by marked hypotonia, failure to thrive, and global developmental delays. Food-seeking behaviors, growth-hormone insufficiency, cognitive disabilities, and neuropsychiatric/behavioral issues become prominent during school-age years.[1-3,5] Temper tantrums, stubbornness, compulsive-like behaviors, and difficulty with changes in routine are hallmark behavioral symptoms that affect 70% to 90% of youth with PWS.[4] Additionally, sleep abnormalities are common in individuals with PWS and can include sleep-disordered breathing, abnormal circadian rhythms in rapid eye movement sleep, reduced rapid eye movement latency, and EDS.[4,20]

Deficits of the wake-promoting peptides, hypocretin (orexin) and histamine, play a key role in the development of narcolepsy and EDS associated with a variety of neuropsychiatric disorders, including PWS.[21,22] Histaminergic neurons clustered in the posterior hypothalamus and those that project broadly throughout the CNS promote wakefulness, attention, and cognition.[22,23] Specifically, H3 receptors are thought to be located both presynaptically as autoreceptors on histaminergic terminals and as heteroreceptors on neurons that regulate the release of dopamine, glutamate, and acetylcholine.[23] Given such diverse CNS effects, the H3 receptor has been studied in a variety of neuropsychiatric conditions including Alzheimer disease, schizophrenia, attention-deficit/hyperactivity disorder, Tourette syndrome, and EDS associated with Parkinson disease, and epilepsy.[16,23] Additionally, a recent case series described decreased daytime sleepiness and improved cognition in 3 pediatric patients with PWS.[24]

As a histamine H3 receptor antagonist and inverse agonist, pitolisant quickly crosses the blood brain barrier, resulting in a widespread release of histamine throughout the CNS in addition to other wake-promoting neurotransmitters (e.g., dopamine, norepinephrine, and acetylcholine) throughout the cerebral cortex. Two pivotal placebo- and modafinil-controlled trials led to the 2015 European Union approval of pitolisant in adults with narcolepsy with or without cataplexy.[13,22,25]

Although pitolisant is not currently approved by the FDA for any neuropsychiatric indication in the United States, it is available through an FDA expanded access ("compassionate release") program. Interest regarding the use of pitolisant in pediatric patients with PWS originates from the Chion Foundation's "Pitolisant Program" and their hypothesis that the medication will "normalize sleep, behavior, and cognition."[26] The Chion Foundation is a non-profit organization that is committed "to improv[ing] the quality of lives of families touched by Prader-Willi Syndrome (PWS) and other rare diseases… through identifying new drugs, funding research into the safety and efficacy of those drugs, and facilitating patient access to new drugs."[26,27] They have partnered with the Trend Community to start the Pitolisant Health Initiative that is investigating the role pitolisant in patients with PWS. This program aids families in procurement of the medication through working with the FDA's compassionate release process.

Given the complex combination of neuropsychiatric symptoms among pediatric patients with PWS and pitolisant's unique mechanism of action, this H3 receptor antagonist/inverse agonist may play a unique role in the management of PWS. Currently, antidepressants and antipsychotics are among the most commonly prescribed psychotropic medications for patients with PWS. These classes of medications have not been shown to systematically improve neuropsychiatric symptoms in this population and can be associated with significant adverse effects.[6]

Antidepressants, particularly SSRIs, are frequently used to target ongoing symptoms of obsessive-compulsive disorder, anxiety disorders, and mood disorders in individuals with PWS. Despite widespread use, consistent evidence is lacking in addition to concern that these agents may worsen irritability among youth with neurodevelopmental disorders, particularly at high doses.[28] Antipsychotics are commonly used to target ongoing aggressive behaviors and as augment to antidepressants for obsessive-compulsive behaviors. It is well known that atypical antipsychotics (e.g., olanzapine, risperidone) are associated with significant metabolic concerns, including weight gain, increased blood glucose and lipids, and the development of type 2 diabetes.[29] Youth, compared with adults, are at an increased risk for such effects. This risk may be higher among youth with PWS, who are likely to experience hyperphagia.

Given the lack of evidence to support their use and concern for adverse effects, ongoing evaluation of alternative treatment strategies is needed. This case report describes the use of pitolisant in a 15-year-old with PWS, obsessive-compulsive disorder, autism spectrum disorder, and mild intellectual disability. Since initiation of pitolisant, she has shown positive improvements in attention, cognition, EDS, behavioral outbursts, and aggression. These improvements have been consistently observed by her parents and teachers and are supported by improvements in behavioral tracking at school and the ABC-C rating scale, specifically in her lethargy, irritability, and hyperactivity. Most remarkably, her mother has reported a notable improvement in the patient's ability to complete cognitive tasks independently, something that she has not been able to do for many years. Unfortunately, improvement in anxiety symptoms has not been observed.

Pitolisant is commercially available in Europe as 4.5- and 18-mg film-coated tablets. Adult dosing ranges from 9 mg daily to a maximum dose of 36 mg daily with dose adjustments required for renal and/or hepatic

impairment. There is no clear consensus on pediatric dosing.[8] Common side effects associated with pitolisant include insomnia, fatigue, anxiety, irritability, depression, and nausea/vomiting/dyspepsia. Disturbance in attention, hypersomnia, seizures, hallucinations, obsessive thoughts, and hyperphagia have also been reported.[8] Given the potential to worsen underlying neuropsychiatric symptoms, the use of pitolisant must be considered carefully in such patients. Additionally, pitolisant has the potential to prolong the QT interval. It is recommended that an ECG should be obtained at baseline and with subsequent dose adjustments in individuals at risk for QTc prolongation (e.g., concomitant QTc prolonging medications, long QT syndrome, etc.).[8]

Pitolisant is metabolized via phase I metabolism to an inactive metabolite through CYP3A4 and CYP2D6. Close monitoring and potential dose adjustments of pitolisant are recommended for patients taking potent CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) or CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) in combination with pitolisant. Based on in vitro data, pitolisant may induce CYP3A4, CYP2B6, CYP2C, UGTs, and P-gp. Therefore, concomitant use of pitolisant with substrates of CYP3A4 that have a narrow therapeutic window (e.g., tacrolimus) should be avoided. Given the potential to reduce oral contraceptive effectiveness, use of alternative or additional contraceptive methods should be encouraged.[8]

Pharmacodynamically, tri- and tetra-cyclic antidepressants (e.g., imipramine, mirtazapine) and antihistamines (e.g., chlorpheniramine, diphenhydramine) may render pitolisant less effective due to their ability to block histamine release from the H1 receptor. Close monitoring is warranted if co-administration cannot be avoided.[8] Pitolisant could be considered for pediatric patients with PWS with ongoing EDS, behavioral issues, and irritability despite other pharmacologic interventions. Our patient continues to demonstrate an improvement in symptoms, including reduced aggression and behavioral outbursts and improved cognition and attention. Additionally, the initiation of pitolisant has allowed for reduction and elimination of concomitant psychotropic medications. This alone may serve as an indicator of the positive effects of pitolisant.

Our patient tolerated the medication well, though experienced a notable increase in anxiety, restlessness, and irritability for several days following each dose increase. Additionally, hypersalivation and hyperhidrosis were noted to have worsened following the initiation of pitolisant. Of note, these were present at baseline.

Limitations of this case exist in establishing a relationship between symptom improvement and the initiation of pitolisant. Although pitolisant continued to be titrated to a dose of 36 mg daily, other psychotropic medication changes were made concurrently. These changes may independently explain symptom improvement. Additionally, the patient continues to attend special education school with specialty in managing developmental and behavioral concerns.

Conclusions

This case report describes safe and effective use of pitolisant in a pediatric patient with PWS, obsessive-compulsive disorder, autism spectrum disorder, and mild intellectual disability. Systematic evaluation of pitolisant in PWS is needed to determine specific pediatric dosing strategies, duration of treatment, and long-term effects. Given its unique mechanism of action, pitolisant may reduce the need for concomitant psychotropic medications, thereby reducing the risk for long-term adverse effects (e.g., weight gain, type 2 diabetes associated with atypical antipsychotics), improving both neuropsychiatric and metabolic outcomes for patients with PWS.

Article Information

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