Neurobehavorial Aspects of Prader-Willi Syndrome

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\begin{itemize}
    \item Grant: FPWR
    \item Consultation: Soleno
    \item Scientific Review Board: PWSA, FPWR

    \item Non-FDA indicated use of FDA approved medications is common in psychiatry and will be discussed in this presentation.
\end{itemize}
▪ Recognize the spectrum of behavioral health symptoms (BH) noted in Prader-Willi Syndrome (PWS)
▪ Explain compulsivity, Impulsivity and “response perseveration” as key aspects of BH in PWS
▪ List the commonly used treatment strategies for the management of BH in PWS
▪ Appreciate the need for novel treatment modalities for BH in PWS
- **PWS**: Beyond the loss of function of chr 15 q
- Working with patients and families to draw a timeline
Prader-Willi syndrome

Psychiatric Comorbidities
- ADHD
- Mood Disorders
- ASD
- Psychotic Episodes

Behavioral Features
- Hyperphagia
- Aggression
- Hyperorality

Developmental Features
- Intellectual disability
TIMELINE OF A PATIENT WITH PWS

AGE (IN YRS)

5 6 7 8 9 10 11 11 12 13 14 15

ADHD COMPLAINTS FROM PRE-SCHOOL

PHYSICALLY AGGRESSIVE WITH PEERS- STIMULANT STARTED

STIMULANT DOSE INCREASE- SEVERE ANXIETY

BREAKS DOWN KITCHEN DOOR: ER VISIT- SEVERE LETHARGY WITH LORAZEPAM

WORSENING HOARDING BEHAVIOR

CITALOPRAM DOSE INCREASE FOR ANXIETY/HOARDING

SEVERE AGGRESSIVE EPISODES. SCHOOL CHANGED

VALPROIC ACID ADDED- 15LB WT GAIN IN 2 MO

LOW DOSE CITALOPRAM WITH FAIR RESPONSE

VALPROIC ACID STOPPED DUE TO WT GAIN

SEVERE SKIN PICKING

IMPROVEMENT NAC

LOW DOSE CITALOPRAM WITH FAIR RESPONSE

STIMULANT STOPPED

AFTER SEVERAL TRYS, STIMULANT STOPPED

WORSENED AGGRESSIVE BEHAVIOR WITH PEERS

STIMULANT DOSE INCREASE- SEVERE ANXIETY

BREAKS DOWN KITCHEN DOOR: ER VISIT- SEVERE LETHARGY WITH LORAZEPAM

SEVERE AGGRESSIVE EPISODES. SCHOOL CHANGED

VALPROIC ACID ADDED- 15LB WT GAIN IN 2 MO

LOW DOSE CITALOPRAM WITH FAIR RESPONSE

VALPROIC ACID STOPPED DUE TO WT GAIN

SEVERE SKIN PICKING

IMPROVEMENT NAC
Cycloid Psychosis Comorbid with Prader–Willi Syndrome: A Case Series

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Abstract

Psychosis is a relatively common psychiatric phenomenon seen in patients with Prader–Willi Syndrome (PWS). However, the presentation is atypical and difficult to classify within currently defined affective or psychotic disorders. This distinct presentation may be better understood as a phenomenon called “cycloid psychosis,” described as an episodic psychosis with rapid full recovery between episodes. This study retrospectively analyzed the cases of 12 patients with genetically confirmed PWS who presented to an ambulatory psychiatric center for a change in behavior consistent with psychosis. Each case was then assessed for symptoms of cycloid psychosis, bipolar disorder, depression with psychotic features, schizophrenia, and schizoaffective disorder. Out of the 12 patients, 11 (91.7%) met the currently described diagnostic criteria for cycloid psychosis. Of the 12 patients, 7 (58.3%) also met the diagnostic criteria for bipolar disorder, and 1 (8.3%) also met the diagnostic criteria for schizoaffective disorder. None of the patients met the criteria for schizophrenia or depression with psychotic features. The findings in this study suggest that cycloid psychosis and bipolar disorder may both be comorbid with PWS. Psychiatric comorbidities in patients with PWS are atypical and clinicians should be aware of conditions such as cycloid psychosis when managing this vulnerable population.
DSM-5 Anxiety Disorders:

- GAD
- Specific Phobia
- Separation Anxiety
- Social Anxiety

PWS related anxiety appears to be different
DSM-5 Obsessive-Compulsive and Related Disorders:

- OCD
- Body Dysmorphic Disorder
- Hoarding Disorder
- Excoriation Disorder

PWS related obsessive-compulsive behavior seems to be different
Hard to categorize within DSM-5 constraints
RESPONSE PERSEVERATION: the inappropriate repetition of a particular response despite the absence or cessation of reward.

In PWS:
- Related to **compulsivity**
- Repetitive questioning and intrusive behavior despite negative response by caregivers.

Is it Anxiety? Or is it Impulsivity???
What is the diagnosis???

“Obsessive Compulsive and Related Disorder due to PWS with OCD-like symptoms, hoarding symptoms, and skin-picking symptoms”
The tendency to engage in rash, ill-considered action in response to intense negative emotions

Associated with low volumes of pre-frontal cortex
• RESPONSE MONITORING: The capacity to flexibly adapt to dynamic environments is a crucial component of optimal daily functioning. Dysfunction → Inflexibility

• Acute dorsolateral prefrontal cortex ischemia → Perseveration

In addition to expected hypothalamic and pituitary differences, patients with PWS abnormalities in the prefrontal cortex
• Benzodiazepines
  • E.g. Alprazolam, clonazepam, lorazepam
• Serotonin Receptor Inhibitors
  • E.g. Sertraline, citalopram, fluoxetine
• Antipsychotics
  • Typical e.g. haloperidol, chlorpromazine
  • Atypical e.g. risperidone, aripiprazole
• Mood Stabilizers
  • Lithium
  • Anticonvulsants- valproate, lamotrigine, Topiramate, carbamazepine, oxcarbazepine
Other Medications

- Buspirone
- Mirtazapine
- Bupropion
- NAC
- Early evidence: DCCR (OC sx), pitolisant, CBD
- Alpha-2 Agonists: Guanfacine XR
  - Selective α2 adrenoceptor agonist
  - Moderates left DLPFC activation
  - ADHD- FDA approval
  - Reduces ADHD/impulsiveness in autism
  - Most common S/E- sedation/fatigue
Guanfacine Extended Release for the Reduction of Aggression, Attention-Deficit/Hyperactivity Disorder Symptoms, and Self-Injurious Behavior in Prader-Willi Syndrome—A Retrospective Cohort Study

Deepan Singh, MD, Yuji Wakimoto, BS, Carole Filangieri, PhD, Aaron Pinkhasov, MD, and Moris Angulo, MD

Abstract

**Objective:** To examine the role of Guanfacine Extended Release (GXR) in the management of behavioral disturbances in patients with Prader-Willi Syndrome (PWS).

**Methods:** Twenty from a total of 27 individuals with genetically confirmed PWS, 6–26 years of age, with the following symptoms were identified: significant aggression/agitation, skin picking, and/or symptoms of attention-deficit/hyperactivity disorder (ADHD). Response to GXR for the above noted symptoms was categorized as improved, worsened, or unchanged, while assessing for side effects and tolerability.

**Results:** Eleven of the 20 individuals reported skin-picking, 17 reported aggression/agitation, and 16 reported symptoms of ADHD. Nine (81.8%), 14 (82.3%), and 15 (93.7%) individuals showed an improvement in skin-picking, aggression/agitation, and ADHD, respectively, while on GXR treatment. Two patients with prior complaints of psychotic symptoms did not respond to GXR. Of note, no abnormal weight gain or significant adverse reaction was observed in this group, while on GXR.

**Conclusions:** In this study, GXR demonstrated improvement in symptoms of skin picking, aggression/agitation, and ADHD in patients with PWS. GXR was not effective in reducing psychosis or agitation related to psychotic symptoms. Future studies are warranted to further establish the utility of GXR in PWS patients.
This randomized, double-blind, placebo-controlled clinical trial aims to determine whether guanfacine extended release (GXR) reduces aggression and self-injury compared to placebo in individuals with Prader-Willi Syndrome (PWS) with moderate to severe aggressive and/or self-injurious behavior.

In addition, GXR’s tolerability will be assessed by systematically evaluating and documenting adverse events.
Guanfacine XR for Aggression and Self Injury in PWS: A Double Blind Placebo Controlled Trial

Funding Summary

Guanfacine XR (brand name Intuniv) is a medication for ADHD that improves impulse control. Dr. Singh has noted improvements in aggression and self injury in PWS patients in his practice when using this medication. In this study, he will perform a pragmatic clinical trial to evaluate the efficacy of guanfacine for treating these aspects of PWS, and also evaluate the safety and tolerability of the medication in the PWS population.

Theresa Strong, Director of Research Programs, shares details on this project in this short video clip.

- Aggressive behavior and self injury is fairly common in PWS; when present, it can have a significant impact on quality of life for the family.
THANK YOU!!!

GUANFACINE XR
Clinical Trial:
Ask for Dr. Theresa Jacob to Enroll
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