The Role of Medications

For the Management of Behavioral Problems in Prader-Willi Syndrome

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Disclosures

- **Grants**: FPWR
- **Consultation**: Soleno, Acadia, ConSynance
- **Royalties**: *Neurobehavioral manifestations of Prader-Willi Syndrome* (Cambridge)- images will be used in the presentation
- Non-FDA indicated use of FDA-approved medications is common in psychiatry and may be discussed in this presentation
Genetics

Source: FPWR

1:22000 to 25000 live births
RANGE OF SYMPTOMS

Prader-Willi syndrome

Psychiatric Comorbidities

ADHD
Mood Disorders
Psychotic Episodes

Behavioral Features
Hyperphagia
Aggression
IMPULSIVITY

Developmental Features
Intellectual disability
ASD

O/C SX
Response Monitoring:

The capacity to flexibly adapt to dynamic environments.

- **Response Monitoring**
- **Cortex (Model Based)**
  - Planning
  - Judgment
  - Effort Appraisal

- **Subcortex (Model Free)**
  - Emotion
  - Drive
  - Arousal

- **Uncertainty**
- **Extrinsic stimuli**
- **Intrinsic stimuli**

**Behavioral Response (Decision)**
- Adaptive
- Maladaptive

- Response Perseveration
- Anxiousness
- Impulsive Aggression
- "Getting Stuck"
- Confabulation
- Skin/Rectal Excoriation
Response Perseveration

- 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?
Is it Impulsivity?
Or is it Response Perseveration?
A Dysfunction Waterfall Model of PWS

Genetics

Magel2, Necdin, IC, SNORD115, SNORD116

Neurobiology

Hypothalamus, Grey & White Matter, Neurotransmitters

Behavioral Manifestations

Impulsivity, Response Perseveration, Cycloid Psychosis
Irritability/Aggression

Sertraline in low doses may have a role
ADHD

- ADHD
  - No EDS → Alpha-agonist → Stimulant
  - With EDS
    - Skin picking or tics? (no) → Alpha-agonist
    - Skin picking or tics? (yes) → +/- modafinil
Picking

- Both Topiramate and Naltrexone have added benefit of weighloss
- Topiramate may reduce hyperphagia
Psychosis in PWS

- Not schizophrenia although in some cases might persist
- Sudden, alarming change in behavior
- Sleep disturbance, catatonic symptoms
- Confusion, voice-hearing, paranoia
- Rapid response to treatment
Psychosis/Mania

- Mania
  - Psychosis present
    - no
      - Antipsychotic or Mood-Stabilizer
    - yes
      - Antipsychotic
- Psychosis
Seeking an Alternate Path- Guanfacine XR

- Selective α2 adrenoceptor agonist
- Moderates left DLPFC activation
- ADHD- FDA approval
- Reduces ADHD/impulsiveness in autism
- Most common S/E- sedation/fatigue
## Interim Analysis Guanfacine XR

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Group</th>
<th>Visit 5 CGI-S Score</th>
<th>Response Y/N</th>
<th>Visit 9 CGI-S Score</th>
<th>Response Y/N</th>
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### Response Rate at Visit 5 (Unblinding)

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<th>Placebo</th>
<th>GXR</th>
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<tbody>
<tr>
<td>Non-Responders: 5</td>
<td>Non-Responders: 1</td>
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<tr>
<td>Responders: 1</td>
<td>Responders: 4</td>
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### Response Rate at Visit 9 (End of Treatment)

<table>
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<th>GXR (Open Label Phase)</th>
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<tr>
<td>Non-Responders: 1</td>
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<tr>
<td>Responders: 7</td>
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</table>
Interim Analysis Guanfacine XR

Self Injury Trauma Scale-Number Mean Composite Score (p=0.008)

Self Injury Trauma Scale-Severity Mean Composite Score (p=0.024)

Visit 1 Visit 2 Visit 3 Visit 4 Visit 5

Placebo GXR Linear (GXR)
### Interim Analysis Guanfacine XR - FPWR

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>B (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ABC</td>
<td>-11.615 (16.27, -6.97)</td>
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<tr>
<td>ABC - Subscale 1</td>
<td>-3.94 (-6.9, -0.99)</td>
<td>&lt;0.001</td>
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<tr>
<td>ABC - Subscale 2</td>
<td>-0.640 (-2.73, 1.45)</td>
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<td>ABC - Subscale 3</td>
<td>-1.28 (-1.72, -0.839)</td>
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<td>ABC - Subscale 4</td>
<td>-5.25 (-6.89, -3.81)</td>
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<td>ESS</td>
<td>4.52 (1.89, 7.15)</td>
<td>&lt;0.001</td>
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Treatment: Guanfacine
A phase 3 device study to reduce temper outbursts in people with PWS

IRB-approved and deemed non-significant risk

STUDY DESIGN

- Monitor temper outbursts; Randomize
  - Continuous stimulation: 4 hours / day
  - Intermittent stimulation: 4 hours / day
  - No treatment

Optional continuation to OLE

Seeking an Alternate Path - tVNS

Intermittent is 28 sec on / 32 sec off; 4 hrs can be split up over the day
PW Research Center @ Maimonides Medical Center
Thank You!

Current PWS Research at Maimonides:
Guanfacine XR
Bright Light Therapy
Hyperphagia (Gedeon-Richter)
tVNS coming soon!
Phone: (718) 283-8170
THANK YOU

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