Pregnenolone Trial in Autism—a Neurosteroid Approach

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Attending Psychiatrist, Pediatric Neuropsychopharmacology Clinic
Co-investigator, “Randomized Controlled Pilot Trial of Pregnenolone in Autism”
Co-investigator, “Cross-Species Multi-Modal Neuroimaging to Investigate GABA Physiology in Fragile X Syndrome”
Stanford University School of Medicine
Neurosteroid Approach to Treat ASD
Excitation / Inhibition Balance

Excitation

Inhibition
Hypothesis: Excitation / Inhibition Imbalance in Autism
Modulating Excitation / Inhibition Imbalance in Autism
Modulating Excitation / Inhibition Imbalance in Autism

![Diagram showing balance between excitation and inhibition in the brain](image-url)
GABAergic System

Pre-synaptic inhibitory neuron:
- Glutam- inase
- Glutamine (Gln) → Glutamate (Glu)
- GAD (GABA synthetase)
- GABA

Post-synaptic inhibitory neuron:
- GABA-A receptors (GABA_A_R)
- GABA-B receptors (GABA_B_R)
- Extra-synaptic GABA_A_R

Glial cell:
- GLS
- GABA-T
- GABA

Phasic currents: GABA-A and GABA-B receptors
Tonic currents: Extra-synaptic GABA-A receptors

Stanford University

Lawrence K. Fung · Robin A. Libove · Jennifer Phillips · Francois Haddad · Antonio Y. Hardan
Neurosteroid Metabolism

- Cortisol
- Corticosterone
- 11\(\beta\) hydroxylase
- P450c17
- 3\(\alpha\)-HSOR
- Estradiol
- Estrone
- Aromatase
- P450c17
- TSPO
- Cholesterol
- Androstanediol
- Allopregnanolone
- THDOC
- P450c21
- CYP2D
GABAergic System

Allopregnanolone, THDOC, Androstanediol

Phasic currents

Extra-synaptic GABA_A R

Tonic currents

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Pregnenolone Open-Label Trial in ASD Adults

• Study design
  – Open-label
  – 10 males and 2 females
  – Dose administration:
    • Week 1 & 2: 50 mg twice daily
    • Week 3 & 4: 100 mg twice daily
    • Week 5 & 6: 150 mg twice daily
    • Week 7 & 8: 200 mg twice daily
    • Weeks 9 to 12: 250 mg twice daily

• Inclusion criteria
  – 18–45 years of age
  – physically healthy males and females who are
  – diagnosis of autistic disorder
  – CGI-S greater than or equal to 4
  – stable concomitant medications for at least 2 weeks (4 weeks if patient took fluoxetine)
  – no planned changes in psychosocial interventions during the open-label pregnenolone trial

• Exclusion Criteria
  – DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder NOS
  – prior adequate trial of pregnenolone
  – active medical problems such as unstable seizures, or significant physical illness (e.g., serious liver or renal pathology)
  – Pregnancy or sexually active females (as determined by a urinary pregnancy test in the beginning of the study)
  – subjects taking oil or fat-based nutritional supplements would be excluded from the study except they had been off these compounds for at least 4 weeks

• Primary Endpoint: Aberrant Behavioral Checklist-Irritability (ABC-I)

# Adverse Events reported in Pregnenolone Open-Label Trial in Adults with ASD

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of patients reporting AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness</td>
<td>1*</td>
</tr>
<tr>
<td>diarrhea</td>
<td>1*, 1#</td>
</tr>
<tr>
<td>depressive affect</td>
<td>1*, 1#</td>
</tr>
<tr>
<td>increased excitement/agitation</td>
<td>3#</td>
</tr>
<tr>
<td>sleep problems</td>
<td>1#</td>
</tr>
<tr>
<td>drowsiness</td>
<td>1#</td>
</tr>
<tr>
<td>anorexia/decreased appetite</td>
<td>2#</td>
</tr>
<tr>
<td>increased motor activity</td>
<td>1#</td>
</tr>
<tr>
<td>sweating</td>
<td>1#</td>
</tr>
<tr>
<td>constipation</td>
<td>1#</td>
</tr>
<tr>
<td>tremor</td>
<td>1#</td>
</tr>
</tbody>
</table>

*may be medication-related

#remote chance to be medication-related

Preliminary evidence from one open-label study suggests that Pregnenolone may be helpful in reducing irritability, social withdrawal, and sensory aberrations in adults with ASD.

<table>
<thead>
<tr>
<th>Clinical Measures</th>
<th>Baseline</th>
<th>Week 12&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Paired t test</th>
<th>Effect size</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberrant Behavioral Checklist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC-Irritability</td>
<td>17.4</td>
<td>7.4</td>
<td>11.2</td>
<td>7.0</td>
<td>2.5</td>
</tr>
<tr>
<td>ABC-Lethargy/Social Withdrawal</td>
<td>18.1</td>
<td>8.0</td>
<td>12.8</td>
<td>8.7</td>
<td>2.3</td>
</tr>
<tr>
<td>ABC-Stereotypy</td>
<td>9.8</td>
<td>5.5</td>
<td>8.7</td>
<td>6.5</td>
<td>0.7</td>
</tr>
<tr>
<td>ABC-Hyperactivity</td>
<td>20.5</td>
<td>16.1</td>
<td>16.1</td>
<td>8.9</td>
<td>1.8</td>
</tr>
<tr>
<td>ABC-Inappropriate Speech</td>
<td>5.8</td>
<td>4.3</td>
<td>4.8</td>
<td>4.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Short Sensory Profile – Total Score</td>
<td>137.7</td>
<td>21.5</td>
<td>147.6</td>
<td>15.3</td>
<td>-3.2</td>
</tr>
<tr>
<td>Social Responsiveness Scale – Total Score</td>
<td>84.9</td>
<td>8.1</td>
<td>84.5</td>
<td>9.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Vineland&lt;sup&gt;b&lt;/sup&gt; – Adaptive Behavior Composite Score</td>
<td>37.3</td>
<td>13.1</td>
<td>42.9</td>
<td>16.5</td>
<td>-1.3</td>
</tr>
</tbody>
</table>

* p < 0.05
<sup>a</sup> Week 12: end of the active treatment phase
<sup>b</sup> Vineland: Vineland Adaptive Behavior Scales

Plasma Concentrations of Neurosteroids at Baseline and after a 12-week Treatment of Pregnenolone

<table>
<thead>
<tr>
<th>Neurosteroid</th>
<th>Baseline conc (ng/mL)</th>
<th>Week 12 conc (ng/mL)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnenolone</td>
<td>1.9±.7</td>
<td>7.0±4.1</td>
<td>.00029</td>
</tr>
<tr>
<td>Pregnenolone sulfate</td>
<td>28±14</td>
<td>134±104</td>
<td>.0022</td>
</tr>
<tr>
<td>Progesterone</td>
<td>.38±.09</td>
<td>.56±.19</td>
<td>.0067</td>
</tr>
<tr>
<td>Allopregnanolone</td>
<td>.15±.18</td>
<td>1.0±1.0</td>
<td>.0079</td>
</tr>
<tr>
<td>DHEA</td>
<td>5.5±2.1</td>
<td>7.2±4.3</td>
<td>.21</td>
</tr>
<tr>
<td>DHEA sulfate</td>
<td>239±134</td>
<td>255±131</td>
<td>.77</td>
</tr>
<tr>
<td>Estradiol</td>
<td>.18±.17</td>
<td>.24±.33</td>
<td>.58</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>2.9±2.2</td>
<td>2.8±1.5</td>
<td>.84</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>.011±.008</td>
<td>.010±.006</td>
<td>.92</td>
</tr>
<tr>
<td>Cortisol</td>
<td>101±42</td>
<td>139±61</td>
<td>.088</td>
</tr>
</tbody>
</table>

Comparisons of Plasma Concentrations of Neurosteroids between Responders and Non-responders after a 12-week Treatment of Pregnenolone

<table>
<thead>
<tr>
<th></th>
<th>ABC-I</th>
<th>Pregnenolone (ng/mL)</th>
<th>Total testosterone (ng/mL)</th>
<th>Free testosterone (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change (0-12 wk)</td>
<td>Baseline</td>
<td>Week 12</td>
</tr>
<tr>
<td>Responders</td>
<td>20.3</td>
<td>±9.1</td>
<td>12.7</td>
<td>±6.0</td>
</tr>
<tr>
<td>Non-responders</td>
<td>14.5</td>
<td>±4.3</td>
<td>-0.2</td>
<td>±5.2</td>
</tr>
<tr>
<td>p value</td>
<td>.18</td>
<td>.0026</td>
<td>.039</td>
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<td>Week 12</td>
</tr>
<tr>
<td>Responders</td>
<td>20.3 ±9.1</td>
<td>12.7 ±6.0</td>
<td>1.5 ±0.4</td>
<td>7.0 ±4.6</td>
</tr>
<tr>
<td>Non-responders</td>
<td>14.5 ±4.3</td>
<td>-.2 ±5.2</td>
<td>2.3 ±0.7</td>
<td>7.0 ±3.9</td>
</tr>
<tr>
<td>p value</td>
<td>.18</td>
<td>.0026</td>
<td>.039</td>
<td>.99</td>
</tr>
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</table>

Conclusions to the PREG Open-label Study

• Pregnenolone was modestly effective and was overall safe and well tolerated in individuals with ASD.

• Baseline plasma Pregnenolone levels were predictive of response (reduction in irritability).

• 12 week plasma Testosterone levels correlated with reduction in irritability.

• The data support further studies in exploring pregnenolone’s effects on reducing irritability, improving social functioning (a core symptom of ASD), and attenuating sensory abnormalities.

  – A pilot Randomized Controlled Trial of Pregnenolone is now funded by the Simons Foundation Autism Research Initiative
Randomized controlled pilot trial of pregnenolone in autism

Antonio Hardan, M.D.
Stanford University

Medications for treating the core symptoms of autism spectrum disorder (ASD) continue to be an unmet need. The only medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of individuals with ASD are effective in treating irritability and associated aggressive behaviors, but these medications can also cause severe long-term side effects such as diabetes and involuntary motor movements. Effective medications with more tolerable side effect profiles are highly desirable.

Antonio Hardan and his colleagues at Stanford University are planning to examine the effectiveness of pregnenolone in the treatment of adolescents with ASD. Pregnenolone belongs to a new class of hormones known as neurosteroids, which have been shown to be effective in treating various psychiatric conditions, including bipolar depression and schizophrenia. Compared with current FDA-approved medications, preliminary data from Hardan’s group in a small open-label study of pregnenolone suggests that this compound represents a potentially effective and well-tolerated agent for treating irritability in individuals with ASD. In addition, preliminary evidence suggests that pregnenolone may be helpful in improving select core ASD symptoms, such as social deficits and sensory abnormalities.

Hardan’s team aims to extend their work by performing a 12-week randomized, double-blind, placebo-controlled pilot trial to examine the effectiveness of orally administered pregnenolone in reducing irritability and associated behaviors in adolescents with ASD. As ASD is a heterogeneous disorder, the team also plans to examine the usefulness of biomarkers (including blood levels of neurosteroids, eye-tracking and brain wave recording) in predicting treatment response and assessing biological changes with pregnenolone treatment. The use of biomarkers may help identify whether a select subgroup of ASD individuals are responsive to pregnenolone. The results of this pilot trial will further clarify the potential utility of pregnenolone as a medical treatment for ASD.

References:

40 participants (age 14-21 years) with ASD

20 participants to receive Placebo
- Placebo
- Placebo
- Placebo
- Placebo

20 participants to receive Pregnenolone
- 60 mg twice daily for 2 weeks
- 90 mg twice daily for 2 weeks
- 150 mg twice daily for 2 weeks
- 210 mg twice daily for 2 weeks
- 250 mg twice daily for 4 weeks

20 participants to have option to receive Pregnenolone
- 60 mg twice daily for 2 weeks
- 90 mg twice daily for 2 weeks
- 150 mg twice daily for 2 weeks
- 210 mg twice daily for 2 weeks
- 250 mg twice daily for 4 weeks

= EEG, eye-tracking, vital signs, NS levels, blood chemistry, rating scales
★ = vital signs, rating scales

Stanford University
Acknowledgments

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Stanford BioADD Lab

Wenchao Sun, Ph.D.
Jay Rajadas, Ph.D.

Division of Cardiovascular Medicine

Francois Haddad, M.D.

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Mosbacher Family Fund

SFARI
SIMONS FOUNDATION
AUTISM RESEARCH INITIATIVE
Pregnenolone Treatment Trial for Individuals with Autism

Stanford University researchers are recruiting individuals with autism to participate in a research study to examine the effects of Pregnenolone, a steroid hormone treatment, on irritability.

Participants must:
- Be diagnosed with an Autism Spectrum Disorder
- Be between the ages of 14 and 21 years
- Be willing to take Pregnenolone for at least 14 weeks and provide blood samples
- Be willing to participate in behavioral and cognitive testing
- Have no serious medical problems

For More Information, Call or Email
650-723-7547
azaleal@stanford.edu
GABAergic Neuroimaging

**STANFORD UNIVERSITY RESEARCH**

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We are conducting an exciting new brain imaging study to help identify new treatments for individuals with Autism Spectrum Disorder or Asperger’s Disorder.

**Participation in the study will involve:**
- Traveling to Stanford for 3 days
- Remaining still in a simulated scan session
- Cognitive testing
- Preparation for PET imaging
- Completion of a combined 1hour PET/MRI scan

**The subject must be:**
- Between 18 and 45 years of age
- Diagnosed with Autism Spectrum Disorder or Asperger’s Disorder
- IQ greater than 70

**Benefits of participating:**
- Results of the cognitive testing
- High resolution pictures of the brain
- An honorarium of $100 for participation

For more information, or to enroll in this exciting opportunity, please contact:

lkfung@stanford.edu (650) 498-9392

For general information about participant rights, contact 1-866-680-2906

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**HEALTHY ADULTS**

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- Completion of a combined 1hour PET/MRI scan

**The subject must be:**
- Between 18 and 45 years of age
- Healthy and without any psychiatric diagnosis
- IQ greater than 70

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THANK YOU!