

## A Pilot Study of Psychotropic Medications in Prader-Willi Syndrome

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People with PWS generally respond well to appropriate and coordinated interventions that help reduce their problem behaviors. Even so, some individuals benefit from psychotropic medications that help them focus, settle, and take better advantage of these behavioral or educational interventions.

We are very grateful to the PWSA(USA) Capraro Grant for supporting a pilot study on psychotropic medications in PWS. This pilot study identified medication use, target symptoms, and perceived effectiveness of medications. We also identified changes in single genes or alleles that belong to a family of genes (CYP450) involved in the first wave of drug metabolism in the liver. Two of these alleles (2D6 and 2C19) produce enzymes that are involved in the metabolism of many psychotropic medications. Changes or polymorphisms in these alleles may explain some of the variable responses to medications that we see in PWS. There is no reason to believe that alterations in the PWS 15q11-q13 region are associated with altered 2D6 or 2C19 status. Much like the general population, however, changes in these alleles may help explain why different people with PWS may react favorably, adversely, or not at all to the same type or dose of psychotropic medication.

For the study, 86 parents completed medication surveys, and we obtained buccal cells (saliva with a swish of Scope mouthwash) for genetic analyses from offspring with PWS aged 8 to 51 years (average = 24 years). CYP450 status was assessed at Vanderbilt, and PWS genetic subtypes were clarified as needed by Dr. Merlin Butler's lab. As noted in Table 1, a full 76% of participants were taking SSRI's, or agents that selectively block the re-uptake of serotonin in the synapse (or how neurons communicate), thereby increasing the amount of serotonin available in the brain. Most participants were taking an SSRI plus another agent(s). Although multiple medications make it hard to tease apart which agent is the most helpful for a specific symptom, parents reported that SSRI's or atypical anti-psychotic medications helped the most with tantrums, irritability and repetitive behaviors. As shown in Tables 2 and 3, neither agent was rated as particularly helpful in reducing skin-picking, food preoccupations or food-seeking.

Regarding CYP450, the Vanderbilt DNA Core used a handful of probes to identify changes in 2D6 and 2C19. These were research-based probes only, and pale in comparison to the numbers of probes now readily available for clinical and

commercial use in the recently marketed, FDA-approved Roche Amplichip CYP450 Test<sup>®</sup>. Although preliminary, we found that most participants were so-called normal, "extensive metabolizers" meaning that they had one or two functional copies of the 2D6 and 2C19 alleles. Some participants with PWS, however, were "poor metabolizers", at rates consistent with the general population (See Table 4). These participants had two non-functional alleles, and would not be considered good candidates for medications that are metabolized using 2D6 or 2C19.

Interestingly, 37% of the PWS sample were identified as "intermediate metabolizers" of 2D6, meaning they had one non-functional allele and 1 allele that had low enzyme activity. It is tempting to conclude that this intermediate category explains why people with PWS often respond better to very low dosages of medication, but researchers in pharmacogenetics do not yet agree on the clinical relevance of this intermediate category.

While CYP450 status may assist clinicians in making appropriate medication choices, how people with or without PWS metabolize psychotropic medication also depends on a host of other factors. These factors include gender, age, diet, ethnicity, diseases and health, and interactions with other medications that may inhibit or promote drug metabolism. All of these variables need to be carefully considered by psychiatrists or physicians as they make decisions about medication trials.

In the weeks ahead we will be submitting this study for publication, and working with our psychiatric colleagues to create a tip sheet for psychiatrists and other prescribing physicians who treat people with PWS. In the meantime, we end with some general rules of thumb, and some excellent resources regarding CYP450 testing and people who have "dual diagnoses", or co-occurring intellectual disabilities and psychiatric or behavioral disorders. We again thank the PWSA(USA) for their support, the many families who participated in this project, Merlin Butler for genotyping participants, and Cara Sutcliffe in the Vanderbilt DNA Core.

### **General Tips**

When possible, judge the effectiveness of one medication before adding others to a trial. This approach will help later when you want to taper medications that don't seem to be effective.

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Begin with small doses, and increase doses very slowly. In general, decrease doses when there are signs of adverse reactions or loss of beneficial effects. Stop the trial if symptoms worsen considerably, or if they stay worse and do not improve.

Individuals with PWS are partners and stakeholder in their medication trials. Expect them to share how they think the medication affects their thoughts, mood, or behavior.

Medications are most effective when used in conjunction with behavioral or other therapies. A good response to medications is not a reason to discontinue or reduce behavioral, educational, recreational, speech, or other interventions. Medications may help people take better advantage of more intense intervention or instruction.

Document what you observe during the trial, including any changes in mood, behavior, sleep, etc. Ask your physician for a checklist to help guide your observations.

Communicate with your prescribing psychiatrist or physician. Communication often wanes after the trial is under way. Have a plan for how often you will stay in touch even when the trial is going well and target symptoms are stable. This is important as the same medication may not work continue to work as well over an extended period of time.

Ensure that all members of the intervention team are aware of the medication trial, and of the symptoms being targeted.

New medications are continually being developed, with fewer or different side effects. Even if a previous medication trial did not work well, check in with your physician or psychiatrist from time to time to see if newer agents may be of help.

Consider working with your physician to obtain the CYP450 allele status of your child or client, see resource below. Allele status is just one of several factors to consider in planning a medication trial, and may be especially helpful for individuals with previous unsuccessful trials.

### Key Resources:

Roche Amplichip CYP450 Test; [www.amplchip.us](http://www.amplchip.us)

De Leon, J., Armstrong, S., & Cozza, K., (2006). Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics*, 47, 75-85.  
(a very helpful overview and summary)

[www.theNADD.org](http://www.theNADD.org)  
(excellent books, DVDs, and other resources on diagnosing, treating and supporting people with intellectual disabilities and psychiatric or behavioral concerns)

Fletcher, R., Loschen, E., Stavrakaki, C., & First, M. (Eds). (2007). *Diagnostic manual-intellectual disability: A textbook of diagnosis of mental disorders in persons with intellectual disability*. Kingston, NY: NADD Press.  
(a new manual with adapted diagnostic criteria for making psychiatric diagnoses in people with intellectual disabilities)

Szymanski, L., & King, B.H. (1999). Summary of the practice parameters for the assessment and treatment of children, adolescents and adults with mental retardation and comorbid mental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38, 1606-1610.

**Table 1.** Rates of medication use in PWS sample

SSRI's alone	33%
SSRI + anti-psychotic	17%
SSRI + anti-psychotic + anti-convulsive	17%
SSRI + anti-anxiety or anti-depressive	9%
Atypical anti-psychotics	11%
Anti-psychotic + other	12%

**Table 2.** Parental or care provider responses regarding the helpfulness of SSRI's

	No	Yes
Tantrums	14%	86%
Skinpicking	60%	40%
Compulsions	29%	71%
Irritability	14%	86%
Food issues	61%	39%

**Table 3.** Parental or care provider responses regarding the helpfulness of anti-psychotics

	No	Yes
Tantrums	4%	96%
Skinpicking	47%	53%
Compulsions	37%	63%
Irritability	7%	93%
Food issues	72%	28%

**Table 4.** 2C19 and 2D6 status for poor or intermediate metabolizers

	Poor Metabolizers		Intermediate Metabolizers
	2C19	2D6	2D6
Caucasian population	2-4%	5-10%	?, unknown
PWS pilot study	3.2%	2.5%	37%