Prader-Willi SYNDROME ASSOCIATION (USA)
SAVING AND TRANSFORMING LIVES

Psychotropic Medication Tip Sheet for Patients with Prader-Willi Syndrome for Health Care Providers

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Prader-Willi syndrome (PWS) is caused by the absence of expression of paternally derived genetic material to chromosome 15q11-q13 and it occurs in about 1 in 15,000 births. There are three main subtypes of PWS: 70% of cases are due to a deletion of the PWS region on the paternal chromosome 15, and 25% to maternal uniparental disomy (UPD), or when the child inherits both 15 chromosomes from the mother and none from the father. Approximately 2-3% of cases are caused by imprinting mutations (IM) which silence the expression of the critical PWS 15q11-q13 region.

Knowing the genetic subtype is increasingly important, as certain behavioral and psychiatric characteristics are more common in one subtype versus another. Those with UPD, for example, are more apt to show autistic tendencies or autism spectrum disorder, and as they get older, to manifest psychosis or affective disorders. Severe psychiatric illness in cases with UPD likely relates to the overexpression of maternal genes in the 15q region, while psychiatric problems in those with deletions seem related to family history. Across subtypes, behavioral or psychiatric flare-ups also relate to stress, environmental changes, and having fewer problem-solving or coping skills than those without intellectual disabilities.

The characteristic physical features of PWS include hyperphagia, food seeking, risks of obesity, and increased pain threshold. Behavioral characteristics include intellectual disabilities, cognitive inflexibility, rigid repetitive behaviors, tantrums, oppositionality and skin-picking. Much focus has been on hyperphagia and food seeking in PWS, which do not typically respond to pharmacological treatments. Yet most parents and caregivers express more concern with the behavioral features of PWS, as these often impede optimal daily living and can pose significant management challenges for families. Many families caring for children and adults with PWS will seek psychiatric treatment for problems such as mood lability, tantrums, skin picking and repetitive behaviors.

Most psychiatrists will not have treated more than one or two cases with PWS. More important than previous experience is a willingness to learn about the management of the clinical features of PWS. Patients with PWS will require more time for the initial evaluation and will need to be carefully monitored and seen with their parents or caregivers, as these informants provide data regarding presenting problems, environmental stressors, concurrent medical problems timelines, etc. Patients with PWS often have limited insight or social judgment, and while they can share their thoughts and feelings, they need help identifying more abstract information related to treatment goals.

Many guidelines used to treat people with intellectual disabilities in general also apply to those with PWS. In this population, for examples, behavioral or psychiatric episodes may relate to untreated pain or medical conditions (e.g., constipation, UTI, dental caries), change in daily routines (e.g., a teacher is ill, activities are not as planned), or emotional upsets related to loss or change (e.g., pet dies, staff member moves, exaggerated grief reactions). Additional tips that optimize psychiatric work in those with intellectual disabilities involve basic communication. It is often best, for example, to take the lead from parents as to how to best communicate with the patient, to use simple words, speak slowly without shouting, use visuals as needed, and talk directly to patients instead of referring to them in the 3rd person while in ear shot of their parents or staff. The personality strengths and hobbies of those with PWS can also be used in the service of their treatment.

Behavioral interventions are a critical feature of treatment in PWS; they should be tried before psychotropic medications are used, and in combination with all medication trials. Functional behavioral assessments or input from an applied behavior analyst are highly recommended. The goal of behavioral assessments may be to change the environmental conditions rather than expecting the person with PWS to change. In addition to an individualized behavioral plan, more general supports that work well in people with PWS include daily routines, visual schedules, and positive rewards instead of punishments. Psychiatrists are

critically important to the success of the individual's treatment team, which often includes behavioral, educational, residential, and occupational specialists who are less familiar with medications or side-effects.

Psychotic symptoms often emerge in young adulthood and may be missed due to unusual premorbid social functioning and reduced abilities to articulate changes in mood or thoughts. Precursors can be subtle, including a worsening in self -care or grooming, changes in sleep and eating patterns, increased withdrawal or sadness, and the onset or worsening of intense or odd preoccupations. Often the insatiable drive to eat may disappear as psychotic symptoms emerge. It is unknown if persons with PWS are prone to reoccurring episodes throughout adulthood, but early identification and treatment of symptoms is a critically important step in optimizing outcomes. Symptoms can be exacerbated by stress and looking to the environment for clues (loss, grief) is often helpful. Psychotic episodes may require brief hospitalization to treat effectively. If so, it is critically important to ensure food supervision during hospitalization.

In a pilot study of 86 individuals with PWS who were currently prescribed medications, Dykens and Roof found that 76% were taking an SSRI and most were taking an SSRI along with other medications such as an atypical antipsychotic. Parents reported that SSRI's or atypical antipsychotic medications helped the most with tantrums, irritability and repetitive behaviors. Neither of these agents was rated as particularly helpful in reducing skin picking, food preoccupations or food seeking.

Medications commonly used in people with PWS include SSRI's to target irritability, perseverative behaviors, tantrums and depressed mood. Mood stabilizers (lithium, depakote, carbamazine) can target mood lability and outbursts. Atypical antipsychotics (respiridone) have proven effective in aggression, impulsivity and anger outbursts in PWS. A typical side effect from these medications, weight gain, is less common in PWS, perhaps due to high levels of food supervision in PWS. Some side effects (extrapyramidal) are more difficult to assess due to hypotonia, poor temperature regulation and sleep abnormalities in PWS. Long acting stimulants can help settle and focus some patients with PWS, allowing them to take better advantage of educational opportunities or therapies. Most individuals with PWS do not present with classic hyperactivity (and are instead prone to under activity and daytime sleepiness), but may be distractible and inattentive in the classroom or in social settings. Small doses of long acting stimulants may prevent irritability and increase focus during school hours. Careful attention should be paid to an increase in repetitive behavior or skin picking, or the emergence of tics. Though many typically-developing children may lose weight or appetite with stimulants, weight and appetite in those with PWS is not usually affected.

Some classes of medication (SSRI's and neuroleptics) are more likely to have side effects at standard doses, possibly as a function of individual drug metabolism differences in PWS. As a general rule, start with small doses and increase slowly watching for possible mood activation or other side effects like agitation or increased irritability. In general, decrease doses when there are signs of adverse reactions or loss of beneficial effects. Clinical lore suggests that patients with PWS respond to unusually low doses of medication. When possible, judge the effectiveness of one medication before adding others to the trial. This approach will help later when you want to taper medications that don't seem effective. Some patients with PWS require more than one medication to control different symptoms. Parents and caregivers need to be informed about possible adverse reactions or drug interactions as they monitor effectiveness. CYP450 testing to assess individual drug metabolism can be very helpful, especially in patients who have not responded well to previous medication trials.

In addition to appointments or calls, a good way of staying in touch with families and patients during treatment is through checklists or diaries that track information about mood, sleep, behavior and thoughts. Families who seek psychiatric care should keep a diary of every medication visit including the medication prescribed, dosage used, symptoms targeted and reason why discontinued. It is important to let parents know that some medications may lose effectiveness over time, or that sometimes several medications will be tried before finding just the right

combination. Expect patients with PWS to give feedback on how medications or dose changes may affect their sleep, moods and behavior and to be a stakeholder in this process. Listening carefully to their feedback can help ensure better patient compliance and success.

Key Resources:

Psychiatric Primer by Forster and Gourash

Roche Amplichip CYP450 Test; www.amplichip.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
(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 co-morbid mental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 1606-1610.

PWSAUSA.org has an excellent database of archived materials, books, and manuals about PWS. The PWSA Clinical Advisory Board can help address specific concerns and make referrals.