The Identification of Psychotic and Affective Symptoms in Adults With Prader-Willi Syndrome

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Psychotic and affective disorders reportedly affect approximately 10% of the adult population of persons with Prader-Willi syndrome. Psychiatric disturbances often are expressed as an episodic worsening of compulsivity, irritability, and noncompliance. Severe symptoms may include hallucinations, anti-social behavior, withdrawal, and food refusal. The classifications of behavioral fluctuations, refusal, and delusions may represent diagnostically distinct psychiatric disorders (i.e., affective disorder, psychotic disorder) or may represent a common neuropsychiatric disorder (e.g., a behavioral phenotype) mediated by individual differences in genetics, environment, and emotional capacities. Serotonin reuptake blockers, antidepressant medication, and antipsychotic medications have been used with varying success to treat psychosis in this population.

Keywords: affective disorders, developmental disability, dual diagnosis, intellectual disability, mental retardation, mood, Prader-Willi syndrome, psychiatric disorder, psychosis, serotonin

Prader-Willi syndrome is a distinctive genetic disorder first described by Down¹² and at a later date by Prader, Labhart, and Willi.²¹ Intellectual and adaptive behavior deficits are common among persons with Prader-Willi syndrome, although not all people with the syndrome have intellectual deficits.¹¹ The most striking and easily identified behavioral manifestations of the chromosomal disorder are an intense preoccupation with food and marked abnormalities in satiety.¹³,²⁹ In addition, persons with Prader-Willi syndrome typically display severe behavioral difficulties not related to food seeking that include irritability, lethargy, impulsiveness, obsessive behavior, temper tantrums, stubbornness, argumentativeness, and self-injurious behavior.⁹,¹³,¹⁶

The purpose of this paper is to review current findings in the diagnosis of psychosis and affective disorders among persons with Prader-Willi syndrome. The behavioral manifestations of the Prader-Willi syndrome genotype and mental illness overlap yet appear to be distinguishable. Specific patterns of onset and clinical manifestations are distinctive features of psychiatric disturbance among persons with Prader-Willi syndrome and may be clinically useful indicators to clarify diagnoses of behavioral disturbances in these adults.

The Behavioral Phenotype of Prader-Willi Syndrome

The behaviors typically associated with Prader-Willi syndrome are well documented.¹⁷ The expression of both non-disruptive and disruptive phenotypic behaviors varies between individuals both in the number of typical behaviors manifested and in the intensity of expression.¹ The frequency and intensity of the phenotypical behaviors are mediated by many individual factors, including the source of the genetic miscoding, the presence of delays in cognitive and physical abilities, environmental pressures, education and training, and family and community support.¹⁷

The changes in clinical presentation that occur in young children (e.g., physical changes such as delayed sexual maturation, behavioral changes such as insatiability, emotional changes such as mood fluctuations) are a persistent and well-documented feature of the syndrome.¹⁷ Likewise, adolescence is associated with an increase in emotional lability and an increase in compulsive and obsessive behaviors.⁹,²⁸ Descheemaeker et al.¹⁰ describe two patterns of disruptive behavioral development frequently observed in children and adolescents. The first, active and extrovert, describes a developmental pattern of maladaptive behaviors that progresses...
from low tolerance for frustration, rigidity, and temper tantrums in childhood to agitation, obsessions, mood instability, and cyclical exacerbations of eating, emotional lability, and self-neglect in young adulthood. The second, passive and introvert, describes a developmental pattern that progresses from underactivity, overtiredness and withdrawal in childhood to a cyclical pattern in young adulthood of eating and sleeping disturbances, irritability and aggression, and dysphoric mood suggestive of a bipolar disorder.

While the development of children and adolescents with Prader-Willi syndrome is characterized by often dramatic changes, the typical development of adults with Prader-Willi syndrome has not been described. While disruptive symptoms appear to increase with age, there is a lack of research on the life course of older persons with Prader Willi syndrome, although many reports in the literature do contain data that is inclusive of individuals 40 or more years of age. Although it is unclear if adults with Prader-Willi syndrome display behavioral changes as they age, it is clear that adults with Prader-Willi syndrome, when matched with peers who display similar cognitive abilities, have a significantly greater number of behavioral problems. There may be an association between the degree of cognitive impairment and the severity of disruptive behaviors, adaptive skills, and age; further research is needed.

**Psychotic and Affective Symptoms Among Persons With Prader-Willi Syndrome**

Neuropsychiatric disorders among adults with Prader-Willi syndrome are tentatively classified into three manifestations that are useful in identifying behavioral targets for treatment. These classifications are: (a) trait fluctuations (i.e., behavioral and vegetative states including antisocial behaviors, sleep disturbances, and weight loss), (b) lethargic-refusal (i.e., self neglect, isolation, refusing food or drink), and (c) delusional psychotic thinking (i.e., auditory hallucinations, mood disturbances, delusions, agitation, hyperphagia, and declines in attending behavior and functional skills). The intensity of the expression of these manifestations varies among persons diagnosed with Prader-Willi syndrome. It is unclear as to whether the classifications of behavioral fluctuations, refusal, and delusions represent diagnostically distinct psychiatric disorders (i.e., affective disorder, psychotic disorder) or represent a common neuropsychiatric disorder (e.g., a behavioral phenotype) mediated by individual differences in genetics, environment, and emotional capacities, each of which may be further influenced by the degree of cognitive impairment. Symptoms such as repetitive behavior, emotional outbursts, and withdrawal, which often manifest in adolescence across many diagnostic groups, such as Prader-Willi syndrome, Down syndrome, autism, and mental retardation, may reflect similarities in neurocognitive functioning in the face of environmental pressures rather than biogenetics. Ongoing longitudinal studies across these diagnostic groups at multiple cognitive and adaptive levels are needed to identify the significance of behaviors and their particular genetic and phenotype associations.

The clarity of the diagnostic process is further impaired as symptoms of psychotic thinking are often included as a feature of affective disorder in those with Prader-Willi syndrome, a finding which suggests that delusions, hallucinations, and agitation may represent a unique symptom cluster associated with affective disorders in persons with Prader-Willi syndrome. Anecdotal evidence that psychotic symptoms displayed by persons with Prader-Willi syndrome respond to antidepressant treatment provides further indication that these symptoms may be typical of depression among persons with Prader-Willi syndrome. Other authors note that psychotic features are not typical of depression in persons with other forms of intellectual decline and that research does not support a unique symptom profile of depression for persons with Prader-Willi syndrome.

Psychotic and affective features manifest themselves in young adulthood, often prior to age 20. Investigations of psychotic and affective disorders among adults with Prader-Willi syndrome indicate that males and females appear to be equally at risk to develop disturbances. Descheemaeker and colleagues found that psychotic symptomology was observed more frequently in persons diagnosed with Prader-Willi syndrome who had lower cognitive abilities while symptoms of bipolar disorder were observed more frequently in this population among persons with borderline to normal cognitive intelligence. However, a link between cognitive level and psychiatric symptomology is unclear and further research is needed. Boer and colleagues reported that the pattern of deletion in chromosome 15...
might be associated with the development of psychotic symptoms in early adult life; individuals with maternal uniparental disomy may be at greater risk. Conversely, Descheemake et al. concluded that the presence of psychiatric symptoms does not appear to be related to the underlying genetic disruption.

Affective states frequently include a cyclical pattern of behaviors described by Bartolucci and Younger as trait fluctuations and lethargic refusal; however, these authors and others note that these cyclical patterns differ from typical depressive disorders in that the person does not report depression. Eating and sleeping disturbances, dysphoric mood, low frustration tolerance, confusion, agitation, and irritability are often reported as symptomatic of affective disorders. Psychotic states may include auditory and visual hallucinations, mood disturbances which include elation and depression, delusional ideas often accompanied by fear, agitation, insomnia, decrease in hyperphasia, a loss of functioning in activities of daily living, as well as paranoid ideation and an increase in obsessive behaviors. Clarke and Verhoeven et al. note that psychosis among persons with Prader-Willi syndrome has a sudden onset and mood incongruent symptoms. Onset does not appear to be associated with medication or brain injury.

**Identification of Psychiatric Disturbances and Emotional Difficulties**

Both psychotic and affective disorders in persons with mental deficits may not be easily classified in terms of existing DSM IV criteria. The applicability and terminology of the diagnostic strategy (i.e., DSM-IV, DRC, ICD-10) may influence the clarity of diagnosis and estimates of the prevalence of psychopathology among persons with Prader-Willi syndrome. In addition, it is unclear whether affective disorders and psychotic disorders represent expressions of a common dysfunction in genetic coding, or diagnostically distinct psychiatric disorders that become increasingly indistinguishable from each other as developmental deficits become more pronounced. The blurring of diagnostic presentation as cognitive and emotional deficits increase is a common problem in providing an accurate diagnosis for persons with mental retardation and mental illness. Symptom patterns may represent differences in the damage to neurochemical processes or represent differences in the expression of symptoms as mediated by cognitive and emotional delays. Further research is needed to confirm preliminary findings that suggest that persons diagnosed with a psychotic disorder tend to have a greater degree of cognitive impairment and tend to display unusual behaviors earlier than persons diagnosed with a bipolar affective disorder. However, clear characteristics distinguish the maladaptive behaviors typical of adults with Prader-Willi syndrome from the maladaptive behavior of adults with Prader-Willi syndrome who display symptoms of a psychiatric disorder.

A key feature in identifying either psychotic or affective disorders in persons with Prader-Willi syndrome is the rapid onset of severe behavior problems atypical of the patterns the person has previously exhibited in the absence of a change in medication, head injury, or other antecedent condition. These behaviors often appear abruptly, without clear history. Symptoms may appear to be organic in nature for repeated examinations of the person and their environment often fail to identify antecedents. Symptomatic behaviors may appear after periods of relatively stable behavior that has been consistent with the phenotype and the individual's developmental level. Episodic exacerbation of phenotypic behaviors is common among persons diagnosed with either psychotic or affective psychopathology; however, persons diagnosed with a psychotic disorder may present with idiosyncratic symptoms such as food refusal. Delusions, visual, and auditory hallucinations are more often reported as symptomatic of persons who are diagnosed with a psychotic disorder than persons diagnosed with an affective disorder. It appears that mental confusion is more typical than hallucinations in affective disorders.

It is unclear the degree to which differentially diagnosing psychosis from an affective disorder is clinical useful in developing an intervention. The literature on the treatment of the phenotypical behaviors of Prader-Willi syndrome primarily consists of case reports. However, the biological mechanisms underlying the obsessive characteristics associated with the syndrome and the potential effect of psychopharmacological interventions in reducing problem behaviors are areas of current interest to researchers. While controlled studies are needed to establish the efficacy of medication treatment, a brief review of the current literature may provide insight into...
treatments that may be of benefit to consumers with Prader-Willi syndrome.

Psychiatric symptoms may be related to the impact of the genetic dysfunction on neurotransmitter systems. Akefeldt, et al. note that individuals with Prader-Willi syndrome have decreased synaptic serotonin transmission and many of the behaviors such as compulsions, irritability, and rigidity seem to be connected to serotonin activity. The genetic dysfunction may alter the synthesis, release, activity, or reuptake of neurotransmitters such as GABAergic, serotonergic, and neuropeptidergic mechanisms. Disturbances in serotonin are implicated as contributing factor to obsessive behavior and psychiatric disturbances. Persons with Prader-Willi syndrome may show altered serotonin function. Benjamin and Boit-Smith and Warnock and Kestenbaum report that serotonin reuptake inhibitors reduce emotional instability and, in some cases, repetitive behaviors such as skin picking. Bartolucci and Younger suggest that most manifestations of neuropsychiatric disturbances in persons with Prader-Willi syndrome may be linked to hyposerotonergic defects associated with the genetic damage. Akefeldt et al. report that people with Prader-Willi syndrome have increased concentrations of serotonin metabolite 5-HIAA in their cerebral spinal fluid suggesting that persons with Prader-Willi syndrome experience an increase in serotonin turnover and possibly decreased serotonin transmission.

Stein and colleagues surveyed 347 individuals with Prader-Willi syndrome and found that serotonin reuptake blockers (e.g., fluoxetine) were the most widely prescribed psychotropic, followed by antipsychotic medications (e.g., haloperidol), stimulant medications (e.g., methylphenidate), and anticonvulsant medications (e.g., carbamazepine). Serotonin reuptake blockers were reported to be helpful in treating temper outbursts and compulsions. Less frequently prescribed were lithium and tricyclic antidepressants. Persons with Prader-Willi syndrome appear to be very sensitive to the sedative effects of haloperidol, developing drowsiness on 2-4 mg per day.

**Conclusion**

Persons with Prader-Willi syndrome may be more susceptible to psychotic disorder. Secondary features of Prader-Willi syndrome, such as sleep disorders, may increase susceptibility to the development of symptoms of psychopathology. Environmental demands may also exacerbate the development of psychiatric difficulty. The stress created by demands for productivity, compliance, and skill acquisition may exacerbate compulsive and other phenotypical behaviors, even though such demands may be consistent with the individual’s cognitive and motor capacities. The severity of cognitive impairment and other neuropsychological patterns of skill acquisition reflecting the subtypes of Prader-Willi syndrome may have complex interactions that place some individuals at higher risk for psychiatric disorder.

Episodic disturbances in affect and behavior are characteristic of persons with Prader-Willi syndrome who are likely to be identified as having a psychiatric disorder. Visual and auditory hallucinations, food refusal, self-neglect, and rapid changes in behavior are obvious indicators that further intervention is warranted. Less obvious indicators such as a cyclical worsening of phenotypic behaviors, increased irritability, stubbornness, or food seeking behavior may be more difficult to ascertain without careful historical documentation of recurring patterns of changes in the intensity and frequency of problematic behaviors. Serotonin reuptake blockers may hold promise as an intervention to reduce the behaviors associated with psychiatric disturbances, although other psychotropic medications such as tricyclic antidepressants and antipsychotics have been prescribed. Persons with Prader-Willi syndrome who manifest psychiatric symptoms typically require highly restrictive and structured levels of care, thus it is important that further research be conducted into the treatment of atypical behaviors in adults with Prader-Willi syndrome in order to improve the quality of life for affected individuals.

**References**


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