

The Mental Health of People with Prader-Willi Syndrome with Specific Focus on Mood Disorders and Psychotic Illness

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Prader-Willi Syndrome (PWS) is a complex genetic condition involving a range of physical, mental health and behavioral characteristics. This fact sheet has been prepared for people with PWS, families of people with PWS and for others who provide clinical, behavioral, and educational support. In the fact sheet the risks for specific mental illnesses, referred to as 'affective disorders' (depression, bipolar disorder) 'psychosis' or 'psychotic illness' and its presentation, course and treatment, are considered. You may wish to share this with your doctor and with others.

Key points covered in the fact sheet

1. The risk of mental illness in people with the different genetic types of PWS
1. The presentation of mental illness and how it can be distinguished from the behaviour difficulties commonly also experienced by people with PWS
1. The characteristic features of mood (affective) disorders and psychotic illness in people with PWS and their diagnosis and treatment
1. Although the mention of mental illness causes concern the factsheet emphasizes the importance of recognizing that such an illness has developed and of having an accurate diagnosis as effective treatments are available.

The problem is often that when an illness develops for the first time, it is not identified, and therefore the most appropriate and effective treatments, which can be started once the diagnosis is made, are not offered. In this factsheet some background information is given before the specific relationship between PWS, mood disorders, and psychotic illness is described, as this is necessary to fully understand the nature of the mental illness in PWS.

The genetics of PWS

A typical person without PWS will inherit one chromosome 15 from the mother and one from the father. Because of a process called genetic (genomic) imprinting, only the genes from the father are active from a specific site on chromosome 15 referred to as 15q11-13. Normally both the mother's and the father's copies of the same genes are both active. However, copies of specific genes at this site (15q11-13) inherited from the mother are quite normally switched off in all of us and are inactive (referred to as being 'imprinted'). If the father's copies of these genes are missing or are also inactivated then neither of the two copies of each of these imprinted genes are present or active and PWS results.

There are therefore three main genetic causes of PWS: a deletion at the specific site on the chromosome 15 inherited from the father (paternal deletion type); inheritance of two copies of chromosome 15 from the mother (the maternal uniparental disomy or mUPD type); and a very rare form referred to as an 'imprinting defect'. These account for approximately 70%, 25% and less than 5%, respectively, of people with PWS, although these rates may be changing.

The behavioral characteristics of PWS

Whilst people with PWS are all individuals and will vary in the nature and extent of their needs, research has identified specific characteristics that are particularly common in people with PWS. Of these the over-eating behavior (hyperphagia) is the best recognized with its origins in early childhood and the risk of severe obesity later on if access to food is not controlled. A tendency for temper outbursts, repetitive and ritualistic behaviors (sometimes referred to as obsessive compulsive behaviors), and skin picking may also be apparent. To varying degrees, this cluster of problem behaviors commonly affect people with PWS regardless of the exact genetic cause and are referred to as the 'behavioral phenotype' of PWS – the term 'phenotype' meaning the outward manifestation of a syndrome of genetic origin.

The mental health of people with PWS

In addition to an increased propensity to phenotypic behaviors described above, people with PWS may experience significant anxiety, particularly at times of change in routine, and may also experience a change in mood. They are susceptible to sustained periods of low mood, sometimes presenting with evidence of depression. Depression is more than unhappiness; it is characterized by at least 2 weeks of being sad, sometimes tearful or irritable. It is usually associated with a significant loss of interest in things that the person would normally have enjoyed; a change in sleep pattern, level of energy and activity; and a decreased ability to perform grooming, hygiene, school or work activities due to impaired concentration and motivation. It is not common to see a reduction in appetite in people with PWS, although it is possible for them to take to their bed and refuse to eat or drink. Loss of self-esteem and a change in the content of the person's thinking may become evident. Feelings of worthlessness, hopelessness and helplessness may lead to ideas that the person is unloved or others are better off without him/her. If the person has made specific plans as to how he/she might harm or

kill him/herself, action needs to be taken to ensure that this cannot happen. This may include continuous supervision and/or admission to hospital.

Sometimes persons with PWS can display a change in behavior due to symptoms of mood elevation that can continue every day for four days or longer. Hypomania (a less severe form of mania) is characterized by increased activity and energy, decreased need for sleep, excessive talking with a tendency to move from one topic to another, and sometimes sustained irritability often associated with an increase in arguments and tantrums. The person may display increased self-esteem and believe that he/she can do things that they are not capable of doing (grandiosity). They may display increased goal directed behavior and engage in behaviors that carry a high risk for painful consequences or a negative outcome. But overall, they are able to continue to perform their activities of daily living, and they do not cause injury to themselves or others. Mania, on the other hand, has all of the symptoms of hypomania, but to a more severe degree and duration. The person's thinking, judgment and level of function become so impaired that they incur negative consequences or injury to themselves or others, and as a result, may require a period of support in hospital.

If variations in mood between high and low repeat over time, this is referred to as Bipolar disorder. When a person's mood fluctuates, it is likely to see an exacerbation of underlying PWS behaviors, such as food seeking, repetitive behaviors, skin picking, argumentativeness or tantrums. These 'mood disorders' (also referred to as 'affective disorders') tend to develop in the teen years and into adult life, and they can affect people with PWS regardless of their genetic sub-type. However, individuals with the UPD subtype are more likely to develop Bipolar disorder. Occasionally, a person with PWS displays a hypomanic or manic mood change while receiving antidepressants for treatment of anxiety, depression or behavior problems associated with PWS. If this pattern of mood and behavioral activation persists after the antidepressant medication is discontinued, then it is likely that the person has an underlying Bipolar disorder.

Psychotic disorder (or psychosis) refers to an illness that is characterized by the emergence of abnormal mental beliefs and perceptual experiences. This includes delusional ideas (fixed false beliefs) such as someone or something is going to harm the person or to influence the person in some way; or hallucinations, such as hearing voices, usually from outside of the head, talking to the person or commenting on the person's thoughts. Sometimes hallucinations can be visual— seeing objects or people who are not there, or tactile – feeling things on the skin that don't exist. These perceptual experiences are very real to the person experiencing them and often frightening. There are other features that can occur, such as the sense that the person's thoughts are being influenced, or it may appear to others that the person's thoughts have become muddled – referred to as 'thought disorder'. When a person with PWS experiences psychosis, he/she can become confused and bewildered, becoming uncertain as to where he/she is or what the date is. Some forms of psychotic illness (particularly those that are related to abnormal mood) can fluctuate over time with changes over days or weeks. It is the change in mood, the presence of abnormal mental beliefs, and the alteration in perceptual experiences that is referred to by the

term 'mental state'. Psychiatric assessment in such circumstances will involve a systematic evaluation of a person's mental state by specifically asking about the presence or absence of the above mental phenomena. Sometimes the person may not be willing or able to describe the abnormal mental experiences that he/she is having, but it becomes apparent through odd comments that he/she makes or how he/she behaves.

The two most common psychotic illnesses affecting the general population are schizophrenia or bipolar disorder – in the case of the latter the disturbance of mood, as described in the earlier paragraph, is also associated with the presence of abnormal mental beliefs and experiences. In people with PWS the manifestations of psychotic illness do not quite fit the recognized characteristics of either of these two disorders, although it is generally considered to be closer to the mood related form of psychotic illness than it is to schizophrenia.

Psychotic illness can affect people with the deletion form of PWS, but it most commonly affects people with the UPD or the imprinting defect form of PWS. Approximately 60% of people with PWS due to UPD may develop a psychotic illness by early adult life, and it is clear that the psychotic illness can develop as early as the teenage years.

Key points: Mood disorders

1. Persons with PWS are stress sensitive, and this confers risk for mood disorders.
1. Mood disorders include Depression and Bipolar Disorder (depression plus hypomania or mania).
1. Antidepressant treatment may result in mood and behavior activation that “uncovers” Bipolar disorder.
1. Psychotic illness is associated with abnormal mental beliefs, perceptual experiences, and deterioration in level of function; it is more likely to occur in adolescence or young adulthood.
1. Psychotic illness can occur with mood disorders, and persons with the UPD subtype or imprinting center defect are more likely to experience “cyclic psychosis” (psychosis with Bipolar disorder).

Diagnosis of psychotic illness in people with PWS

When a psychotic illness occurs, it is associated with marked changes in a person's behavior and 'mental state'. The rate of onset of the psychotic illness can vary from insidious to fairly rapid, and in some cases may evolve over a matter of hours. Families have reported that it may be triggered by stress, such as a change in routine, living situation, admission to hospital or a medical illness, but this is not always the case. When someone with PWS becomes mentally unwell, previous longstanding

behaviors common in people with PWS, such as temper outbursts, skin picking or repetitive and ritualistic behaviors, may become more frequent or increase in severity. Early presenting features of psychotic illness in people with PWS may include a rapidly fluctuating mood, the development of erratic and bizarre behaviours, and the emergence of abnormal mental beliefs or experiences, which are apparent in the content of the person's speech. Occasionally the person with PWS will refuse to eat, or express the belief that the food has been poisoned. Sometimes the person may appear confused and unaware of his/her surroundings.

If someone with PWS develops such problems, a referral to a psychiatrist, ideally a psychiatrist familiar with PWS, is indicated for a comprehensive assessment. This process includes a detailed history from those people (usually family) who have observed the changes. Then, an assessment of the person ascertains whether there is evidence of abnormal mental beliefs or perceptual experiences, indicating the presence of a psychotic illness. One important, and at times difficult aspect of assessment, is checking whether the person with PWS has ideas to harm or kill him/herself. This is of greatest concern where a person has depression and, in that context, is feeling hopeless and he/she may feel others are better off without him or her. If the person has made specific plans as to how he/she might harm him/herself action needs to be taken to ensure that cannot happen. This may include continuous supervision and/or admission to hospital.

If confusion or disorientation is present, it is important to consider whether or not the mental changes might be due to physical illness that has caused a confusional state (sometimes referred to as delirium). If, for example, there were physical symptoms such as a complaint of pain or a history of recent vomiting, then urgent physical assessment is required, as such complaints are rare in people with PWS and are most commonly due to a physical illness.

Key Points: Psychosis

1. Psychotic illness is a form of mental illness that may develop in late childhood or early adult life.
1. Psychotic illness more commonly affects people with PWS due to UPD or those with PWS who have an imprinting center defect.
1. Psychotic illness can present rapidly in association with stress or develop more insidiously, but either way it is associated with a marked deterioration in mood and behavior.
1. Psychotic illness is characterized by the emergence of abnormal mental beliefs such as delusions and altered perceptual experiences such as hallucinations, and sometimes confusion.

1. Changes in a person's mental state and behavior require prompt assessment to eliminate other possible causes. If a psychotic illness is confirmed, effective treatments are available.

This initial process of assessment leads to what is often described by the term 'differential diagnosis' – i.e. developing a list of possible causes which are then narrowed down through further history taking and examination and, if necessary, investigations. It is arriving at the diagnosis and an understanding of all other relevant factors that informs the final clinical formulation and treatment plan.

Treatment of psychotic illness in a person with PWS

Treatment can be divided into the immediate, short-term, and longer term interventions. In the immediate situation, psychiatric guidance should be sought. Once a diagnosis of psychotic illness has been made, it is important to ensure that the person is safe – is their behavior putting themselves or others at risk? Might they harm themselves? Are they eating and drinking sufficiently? How such situations are managed will critically depend on the support network and the nature and extent of a person's problem behaviors. Occasionally, if there is only very limited support available where the person is living and the person has self-harmed or is expressing ideas of self-harm, admission to hospital may be necessary. The immediate response is therefore to ensure the person's safety through support and supervision and to start medication that is known to be helpful in the case of psychotic illness.

When a person is diagnosed with psychosis, medications referred to as antipsychotics, neuroleptics, or major tranquillizers are the treatment of choice to reduce the symptoms associated with the distressing, abnormal mental state, reducing the nature and extent of the hallucinations and delusions and resolving confusion. Systematic evaluations of such treatments for psychotic illness in the general population are considerable, but for people with PWS, who have developed a psychotic illness, the research is limited. However, what research there is suggests that the outcome of treatment for psychotic illness is good.

There is an increasing range of medications available and, as with any form of treatment, the potential benefits need to be balanced against possible risks of side effects. These medications are not for treating 'behavior', rather they are for treating a diagnosed psychotic illness, and as the psychotic illness improves with treatment, so will any associated exacerbation of typical PWS behaviors. Behaviors (such as temper outbursts) that existed before the onset of the psychotic illness will not go away, but the intensification associated with the stress of the illness will return to baseline levels. Because of atypical brain development in people with PWS, there are uncertainties about sensitivity to medications whose action is on the brain (psychiatric medications act on chemical or neurotransmitter systems and their receptors in the brain). Advice is to begin the use of these medications at a lower than typical starting dose and increase gradually and carefully over time depending on the clinical response. All medications have side effects. Antipsychotic medications can affect motor movement to cause

restlessness and agitation (akathisia), tremors (dyskinesias), and muscle stiffening (dystonia). Because of the hypotonia seen in people with PWS, dystonia may present as a loss of facial expression or loss of arm swing arms with arms extended at the side. Most of the time these side effects can be managed by adjusting the dose, but sometimes, additional medications are required to treat them. Because the majority of antipsychotic medications can cause metabolic changes and weight gain, it is helpful to monitor waist circumference and weight. But because most persons with PWS are in settings with controlled food access, weight gain and metabolic changes are less likely to occur. It would be for the psychiatrist to determine exactly which medication to use, but there is international consensus that risperidone is the first line treatment for psychosis in PWS.

Where there is evidence of depression with psychosis, antidepressants, especially those in the SSRI group that also help treat anxiety, may be appropriate. Again their use should be with caution, starting with lower than typical starting doses and increasing carefully. Where there is evidence of mood fluctuations concurrent with psychotic experiences (Bipolar disorder), a combination of antipsychotic and mood stabilizing medications (lithium, carbamazepine, or sodium valproate) may be indicated. But monitoring of potential side effects is essential, such as hypothyroid function with Lithium, low blood sodium levels (hyponatremia) with carbamazepine, and a specific problem relating to ammonia with sodium valproate. The treating doctor should be fully aware of these problems.

Once the immediate presentation has resolved and the person's mental state is improving, then it is helpful to reflect further on whether anything might have precipitated the onset of the illness or might be perpetuating it. Examples include minor physical illnesses; significant changes in, or loss of routine; or increasing levels of stress perhaps following change in accommodation or in the context of some significant life-event, such as bereavement. The task now is to improve the stability of the environment as much as possible so that recovery from the psychotic illness can continue. During this period the medications and doses of medication used will need careful review. As a general rule, once an effective medication regime has been established and the person's mental state is returning to normality, the person should stay on the medication for at least some weeks or even months. If the person's mental state remains stable, the dose can be carefully reduced.

In the longer term the care plan developed to support someone with PWS will not differ significantly from the person with PWS who has not had a psychotic illness. Clearly, controlled food access and food security remain critical to prevent obesity; a structured and quality environment with meaningful activities and good physical health are just as important. If his/her mental state remains unstable or deteriorates, the treatment plan should be revised. There is no doubt that psychological supports to the individual with PWS are important. But interventions such as cognitive behavior therapy (CBT) used for treating anxiety disorder, depression or psychosis in typical persons must be adapted significantly for people with PWS, and the person may not be able to internalize or use these therapeutic tasks autonomously.

Key Points: Treatment

1. Treatment of psychotic illness starts with a detailed history and examination leading to an understanding and an accurate diagnosis, eliminating other possible causes of the deterioration.
1. In the immediate situation, assessment and support should focus on ensuring that the person is safe, and if the person is a danger to his/herself or others, that he/she is supported while possible risks are identified and managed.
1. Psychiatric medications (particularly the class of drugs referred to as neuroleptics, anti-psychotics or major tranquillizers) will need to be given to treat the person's abnormal mental state. The exact medications chosen will depend primarily on the diagnosis.
1. All medications have side effects, and persons with PWS may be more susceptible to adverse events due to atypical brain neurochemistry. Careful selection of medication and monitoring of side effects is essential.
1. Once the mental state is stabilized and the person's behavior is returning to normal, the medication regime should be regularly re-evaluated, ensuring that benefits of the treatment are being maintained and that any side-effects are minimized.
1. In the longer term it is important to maintain food security, to ensure a structured environment, with meaningful opportunities for the person with PWS, and to ensure that those providing support are aware of the person's previous illness, so that if it occurs again, it will be promptly recognized and treated.

Final points

The development of a mental illness such as a mood disorder or a psychotic illness is difficult for all concerned. Not uncommonly the person affected doesn't understand that they have developed an illness and therefore may be unwilling to accept treatment. Sometimes, where someone is very mentally unwell, and particularly if there are concerns about risks to themselves or to others, there are particular laws (depending on the country where the person lives) that might be used to bring someone into hospital without his/her consent in order to provide close supervision and to ensure that he/she takes treatment in the form of medication. Once a person's abnormal mental state begins to improve, he/she may gain some insight and accept the help that is being offered. Then the concerns about risk or the person's behavior will diminish.

Mental illnesses can take different forms, and how such illnesses present and their subsequent course may vary. It is important to work closely with local services to gain knowledge about what is right for each particular person with PWS. Through observation and support over time, it can be determined whether or not on-going

psychiatric medication is needed and, if so, what is the optimum dose, and whether or not the right support plan is in place to ensure a full recovery and a return to a good quality of life.

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