Cognitive and behavioural aspects of Prader–Willi syndrome

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Purpose of review
To provide a review of the recent advances in the diagnosis and treatment of psychiatric disorders in Prader–Willi syndrome (PWS).

Recent findings
Research in the last 12 months has provided a descriptive prognosis of psychosis in PWS and highlighted the possible genes associated with the increased risk of psychosis for those with maternal uniparental disomy (mUPD). Several studies investigating social and communication skills have shown people with PWS to have difficulty with core, receptive and expressive language skills, interpreting emotional valence in faces, playing with children of their own age, understanding personal space and a developmental delay in the theory of mind. These social and communication deficits are often more pronounced in those with mUPD. Two recent clinical trials of oxytocin provide mixed results and highlight the need for an improved understanding of the neurobiological characteristics of the PWS brain. A recent pilot study suggests *N*-acetylcysteine may be a viable treatment for skin picking.

Summary
Recent advances have contributed to our understanding of the emotional and behavioural problems associated with PWS, and provided directions for further research.

Keywords
Prader–Willi syndrome, psychosis, skin picking, social skills, temper outbursts

INTRODUCTION

Prader–Willi syndrome (PWS) is a neurodevelopmental disability characterized by hypotonia and failure to thrive during infancy, then the development of hyperphagia, hypogonadism, cognitive impairments and distinct physical and behavioural characteristics. The behavioural phenotype includes temper outbursts, skin picking, obsessive and compulsive behaviours and mood liability [1–3]. The syndrome is due to a deficiency of paternally expressed genes on chromosome 15 q11–q13, usually as a consequence of a paternal deletion, maternal uniparental disomy (mUPD) or, less commonly, a translocation or mutation of the imprinting centre [4].

PSYCHOSIS IN PRADER–WILLI SYNDROME

Individuals with PWS have an increased risk of developing an affective disorder or psychotic illness, which usually develops in late childhood or early adulthood [5,6,7▪] The course of psychosis is intermittent [6], though a recent study showed that of a group of 20 people with PWS and psychosis, only two had episodes once stability on medication had been achieved. The authors also suggested that given the high rate of mood-related symptoms at the onset of psychosis, reducing the severity of the highs and lows in people with PWS may help to reduce the onset of a psychotic illness [8▪▪]. Such findings highlight the importance of seeking professional help as soon as changes in mood are noted.

People with mUPD present with higher rates of psychosis [3,6], bipolar disorder [7▪] and some autistic-like symptoms [9–11] compared with those with other causes of PWS.

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KEY POINTS

- The prognosis of psychosis in PWS appears to be promising once stability on medication is achieved.
- People with PWS have difficulty with core, receptive and expressive language skills, interpreting emotional valence in faces, playing with children of their own age, understanding personal space and a developmental delay in theory of mind.
- Further work is needed to understand the dysfunction of oxytocin.
- A pilot study suggests *N*-acetylcysteine may be a viable treatment for skin picking.

A recent study provided a possible explanation for the increased rate of psychosis in people with mUPD. The authors hypothesized a two-hit model. First is all people with PWS have an increased risk to an affective disorder, which may in part be due to a small nucleolar (sno)RNA HBIII-52 located in the PWS critical region (15q11–q13) that is known to alter the 2C serotonin receptor [12]. Second, the authors hypothesized that additional expression of the maternal gene increases the chance of developing psychosis. This would be the case for those with mUPD or a deletion but with extra genetic material [8▪▪]. Similarly, Yang *et al.* [7▪] proposed that the increased expression of *UBE3A* in those with mUPD might be a contributing factor to the increased rates of psychiatric illness. *UBE3A* is commonly seen in autism spectrum disorder (ASD) and may also contribute to the increased rate of autism-like symptoms noted in people with PWS [13].

COMMUNICATION AND SOCIAL SKILLS

People with PWS have been shown to display similar repetitive behaviours to those seen in people with ASD [14]. This has led researchers to question whether people with PWS share other primary ASD characteristics, such as social and communication difficulties [15▪,16▪,17,18▪]. A recent study found people with PWS to have core receptive and expressive language abilities within the very low range based on the Clinical Evaluation of Language Fundamentals 4 (CELF-IV) standardization. Both receptive and expressive language skills were lower than would be expected based on the participant's verbal intelligence, as measured by age appropriate Wechsler scales of intelligence. All individuals with PWS showed strengths on the word definition task and weaknesses on semantic relationships, understanding spoken paragraphs and sentence assembly. People with mUPD performed better on expressive than receptive tasks [16▪]. Anyone caring or working with a person with PWS should take these communication deficits and discrepancies into consideration by providing clear succinct sentences and not assuming the person understands, but rather confirming with the person that they have understood what you have said or asked.

There are three recent studies that have investigated social skills in PWS. The first examined social and emotional processing through event-related potential (ERP) responses. ERP data were recorded whilst PWS participants compared the images of social (upright and inverted faces) and nonsocial objects that contained either positive or negative emotional valence. Both genetic subtypes of mUPD were able to distinguish faces from objects but had greater difficulty identifying emotional valence in faces, suggesting that, though able to treat faces as separate to objects, people with PWS have difficulty evaluating facial expressions. Although behavioural responses did not differ between subgroups, those with mUPD showed a similar deficit in brain response (ERP) to processing facial stimuli as has been seen in people with ASD [19]. Finally, the authors compared participants' Autism Diagnostic Observation Schedule (ADOS) scores to ERP findings and found that though while ADOS scores did not significantly differ between genetic subtypes, the scores did correlate with the severity of ERP abnormalities. Overall, this study suggests there may be neural subtype differences in social perception in PWS genetic subtypes, with those with mUPD having abnormalities closer to that seen in people with ASD [17].

Through informer report measures, Dimitropoulus *et al.* [15▪] evaluated social functioning in people PWS compared with a group of people with high-functioning ASD. The authors found that whereas all participants with PWS had difficulty with social competence, only participants with mUPD scored within the same range as those with ASD. For those with a deletion, social responsiveness was correlated with IQ, meaning the higher a person's IQ the less severe the social difficulties. Interestingly, this was not the case for people with mUPD. At least 60% of participants from both subgroups were reported to often or almost always have difficulty with change in routine, perseveration, playing appropriately with children their own age, being aware of other's personal space and not minding not being on the same wavelength as others. For the mUPD group, other clinically significant items included thinking or talking about the same thing repeatedly, knowing when he or she is talking too loudly and showing rigidity or inflexible patterns of behaviour when stressed.

Finally, using the Theory of Mind Test-Revised [20], the third study showed children with PWS have a, median, 4-year developmental delay in the theory of mind, particularly in relation to first and second order belief and false-belief tasks [18▪]. These skills relate to the ability to understand that people have their own thoughts and that these thoughts may differ to their own. The authors suggested that it would be helpful if people caring for or working with people with PWS avoid using figurative speech and name what they were thinking to avoid miscommunication. This study also evaluated individuals with PWS on the Diagnostic Interview Social and Communication (DISCO) disorders and found that although one-third of participants met an ASD diagnosis based on this measure, the most prominent ASD symptoms in the PWS group were maladaptive behaviours and routines, in particular children were most commonly reported to talk to strangers, interrupt conversations, skin pick and literally interpret expressions, suggesting that although people with PWS share some common behavioural features associated with ASD, they may not necessarily display the core behavioural features of ASD.

Overall, these studies show that although all people with PWS have communication and social difficulties, only those with mUPD have difficulties to a similar extent as ASD. However, the proportion of people with mUPD that would meet full criteria for an ASD diagnosis is unknown [13]. Rather it may be more likely that people with mUPD and ASD share some, but not all, phenotypic commonalities.

OXYTOCIN IN PRADER–WILLI SYNDROME

PWS is associated with a reduction in oxytocin-producing neurons in the periventricular nucleus of the hypothalamus [21], which is likely to play a role in several PWS characteristics, including aberrant labour, poor temperature regulation, daytime hypersomnolence, hyperphagia and social impairment [22,23▪]. Two recent studies have investigated the effects of exogenous oxytocin on PWS symptoms. The first, a pilot study, found possible improvements in social abilities in people with PWS after a single dose of oxytocin nasal spray [24]. However, this study did not include a control group or validated measures.

The second study, a randomized double-blind placebo controlled trial, did not find improvement in any of the PWS behaviours measured. Conversely, the authors did find an increase in temper outbursts for those participants on a high dose of intranasally administered oxytocin [25▪]. The authors suggested that as people with PWS have a deficiency in oxytocin-producing neurons, they might also have a deficiency in oxytocin receptors. If this is the case, then the exogenous oxytocin administered may have been binding to oxytocin's hormone sister, vasopressin. Oxytocin is known to have a strong affinity to vasopressin receptors and vasopressin has been shown to play a role in aggressive behaviours, which may provide an explanation for an increase in temper outbursts.

Two recent mice studies suggest that oxytocin binding to vasopressin A1 receptors results in changes in socializing [26], cardiovascular and thermoregulatory activity [27], and symptoms of PWS. The similarity between the PWS phenotype and the physiological and behavioural effect of oxytocin, on both oxytocin and vasopressin A1 receptors, provides strong evidence to suggest that PWS is a disorder of dysfunctional oxytocin. However, more research is needed to determine the exact nature of this dysfunction.

TEMPER OUTBURSTS IN PRADER–WILLI SYNDROME

With a good understanding of the PWS behavioural phenotype, research is now focusing on better understanding individual behaviours. One behaviour that has been of recent interest is temper outbursts. Between 83 and 97% of people with PWS display outbursts [2,3]. Compared with temper tantrums displayed by typically developing young children, PWS outbursts have a later onset, are often more severe and continue to a much later age [28]. The cause for outbursts remains unknown, though Holland *et al.* [3] suggest PWS outbursts might be due to an arrest in development that leads to immature coping skills. This hypothesis was recently supported by a study that showed the behaviours and emotions displayed in PWS temper outbursts are similar to that seen in temper tantrums displayed by typically developing toddlers [29]. On the basis of these findings and the clinical observations of this article's authors, we suggest that this arrest in development is more specifically an arrest or delay in emotional development. Furthermore, we hypothesize that for people with PWS, there is a discrepancy between emotional development and mental age, with emotional development being within similar range to a typically developing 2–3 year old. Research is currently being carried out to test this hypothesis.

SKIN PICKING IN PRADER–WILLI SYNDROME

Miller and Angula [30▪] conducted an open-label pilot study of *N*-acetylcysteine as a treatment for skin picking in 35 people with PWS. The authors

found that after 12 weeks of treatment with *N*-acetylcysteine, 25 participants had complete resolution of skin-picking behaviours and 10 participants showed, though not complete resolution, a significant reduction in skin-picking behaviours based on a reduction in the number of active lesions. The study showed *N*-acetylcysteine to be well tolerated, with only two participants reporting mild side-effects of gastrointestinal upset. Though this study offers promising results, double-blind placebo-controlled trials are needed before clear conclusions can be drawn.

Hall *et al.* [31▪] used functional analysis to examine the environmental determinants of skin-picking behaviours. The authors found that eight of the 12 participants who displayed skin picking during the analysis did so most often when participants were either left alone or in a room with an adult but ignored, suggesting that skin picking was maintained by automatically produced sensory consequences. Given skin picking was reduced when the participant was engaging in an activity, the authors suggested that increasing the access to materials that compete with skin picking may help to reduce these behaviours.

CONCLUSION

Studies from the last year suggest promising outcomes for those with PWS and psychosis. Several genes have been implicated in the high rate of affective and psychotic illnesses in this population, though more research is needed to elucidate the neural link between these genes and behaviours. A surge of interest in ASD symptomatology in PWS has shown that all people with PWS have significant social and communication deficits, which is even more pronounced in those with mUPD. Identifying an individual's social strengths and weaknesses will allow families and professionals working with people with PWS to provide a more supportive social environment for the individual. This may in turn help to reduce some of the maladaptive behaviours seen in this population. A clinical trial of intranasal oxytocin found little benefit to PWS suggesting a need to better understand the neurobiology of the PWS brain. While a recent pilot study suggests *N*-acetylcysteine may be a viable treatment for skin picking.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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