



Prader-Willi Syndrome Through Adolescence and Adulthood

Management with a Focus on Psychiatry

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RareDiseaseDoc · Where compassionate care is always first



Objectives

1

How the phenotype evolves

Describe how behavioral and psychiatric features of PWS change from late childhood into adulthood

2

Genetic subtype matters

Recognize differences in psychiatric risk between deletion and maternal UPD

3

Prescribe carefully

Apply a “start low, go slow” approach to psychotropics, illustrated with clinic cases

4

Plan for adulthood

Anticipate transitions and the medical issues that drive behavior in adults

PWS at a glance

Absent paternal expression of chromosome 15q11.2–q13 leads to hypothalamic dysfunction affecting appetite, sleep, temperature, endocrine function and behavior.



**1 in 10,000–
30,000**

individuals affected



60–75%

paternal deletion
(DEL)



25–40%

maternal
uniparental disomy
(mUPD)



~3%

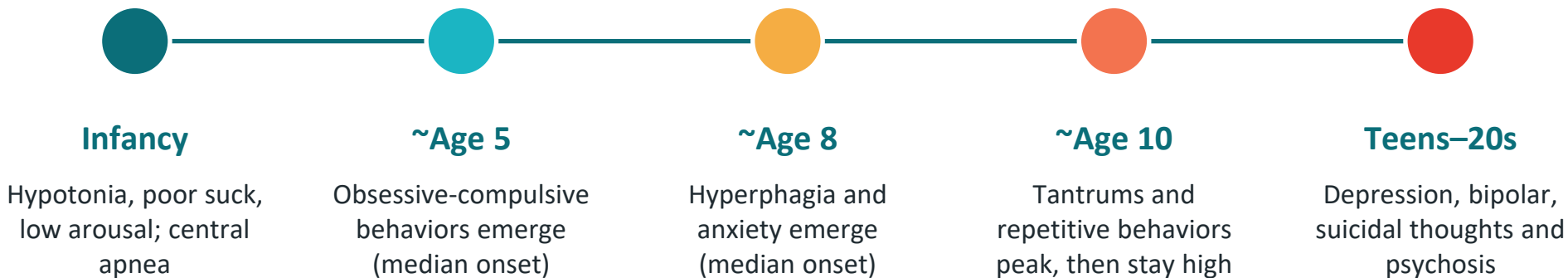
imprinting center
defect (ICD)

01

The phenotype changes with
age



A developmental shift in behavior and mood



Young adulthood: mood disorders with or without out psychosis appears, and its form tracks with genetic subtype.

Six domains define the PWS behavioral phenotype



Food-related drive

Hyperphagia, food seeking, foraging and hoarding



Non-food excessive behavior

Repetitive questions, collecting, hygiene-product overuse



Skin picking

Picking at skin, nose, rectum; other self-injury



Cognitive rigidity

Insistence on sameness; trouble with change



Disruptive behavior

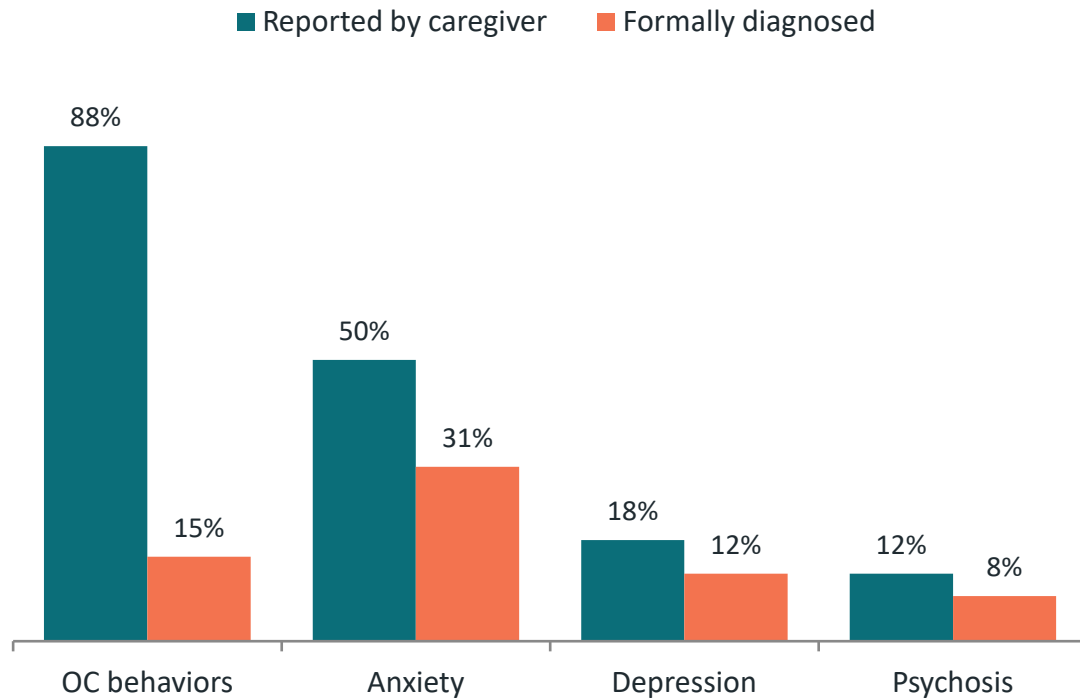
Temper outbursts, aggression, impulsivity



Stress sensitivity & mood

Anxiety, low frustration tolerance, mood change

Symptoms far outpace formal diagnoses



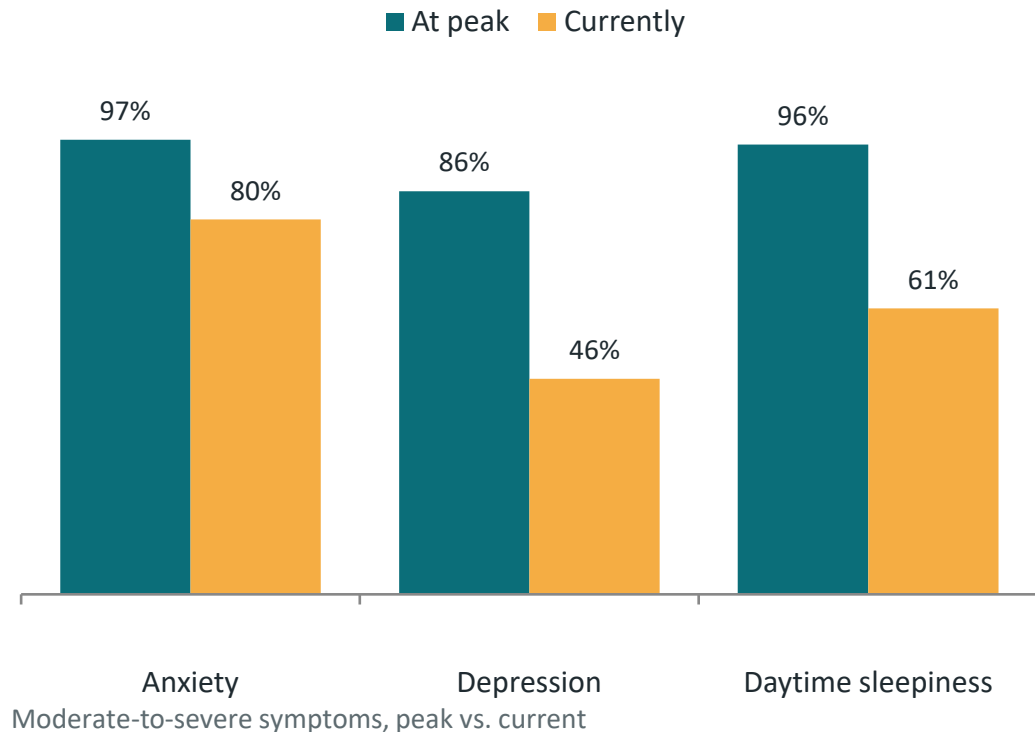
13%

required hospitalization for a mental health issue

55%

reported excessive daytime sleepiness or narcolepsy

Anxiety persists; depression is more treatable



Anxiety

Onset median age 8; fewer than 20% improve to mild or none. Plan for lifelong support.

Depression

Onset in adolescence; severity falls by nearly half, consistent with treatment response.

Comorbidity

Anxiety travels with other psychiatric diagnoses, so screen broadly when it is present.

Genetic subtype shapes psychiatric risk

Paternal deletion

- Seizures more common (18% vs 10%)
- Mood disorder more often unipolar depression, with or without psychosis
- Anxiety and depression risk in young adulthood
- More skin picking and generalized self-injury
- Speech/language learning profile

Maternal UPD

- Psychosis more common (14% vs 7%)
- Cyclic psychosis and bipolar disorder that increase with age; up to ~65% by age 30 in clinic series
- Autism features more frequent, continuing through adolescence
- Higher verbal IQ; nonverbal learning profile
- More repetitive questioning; rectal picking

02

Core psychiatric presentations



Anxiety is the engine behind most behaviors



Break the cycle with security

Food security: no doubt about what, how much and when; no chance to get more. Extend the same predictability to every rewarding item, with routines, picture schedules and clear expectations.

Behavioral outbursts: find the trigger

Common triggers



Blocked access to something wanted



Perceived social injustice or accusation



Changes in routine and transitions



Siblings reaching milestones: driving, dating

New-onset outbursts? Check for:

- A change in routine, setting or caregiver
- Rising anxiety
- Poor sleep, sleep apnea or daytime sleepiness
- A new or recently increased “activating” medication
- Medical causes such as hypoglycemia

In the moment: give space and distract; avoid escalating demands.

Compulsive behaviors and skin picking

88%

have obsessive-compulsive behaviors

15%

formally diagnosed with OCD

Compulsive and repetitive

- Perseverative questioning
- Repetitive actions and routines
- Overuse of hygiene products
- Collecting and hoarding, more in females and adults
- Excessive attachment behavior

Managing skin picking

- Remove the trigger; distract
- Balms or oils; bandages make it worse
- N-acetylcysteine at the height of picking, then stop as it resolves
- Treat the underlying anxiety

Magical thinking or psychosis?

Along the spectrum

- Difficulty separating fiction from reality
- Sensationalizing; ideas rooted somewhere in reality
- Perseverative exaggeration that the person comes to believe and act on



Red flags for psychosis

- Responding to external stimuli
- New indifference to hygiene; slowed movement
- Loss of appetite
- Sleep change and an abrupt change in personality

Clinic vignette

A 10-year-old with UPD perseverated on a superhero film, repeating that he would “save the world,” then tried to board a bus to New York City to do it.

Response: risperidone 0.25 mg markedly improved behavior and delusional thinking.

Psychosis typically emerges in adolescence and is more common with UPD.

Mood disorders and suicidality emerge in adolescence



Depression

Onset in adolescence; reported in 18%, diagnosed in 12%.
Often responds to treatment.



Bipolar and cyclic mood

More frequent with UPD; may present with psychosis and recur with age.



Suicidal and homicidal ideation

Most often begins in adolescence; may follow a destabilizing transition, traumatic event



Safety first

Assess every threat, even when it seems manipulative. Look for the destabilizing event, such as a new caregiver or a sibling's milestone, and address it alongside treatment.

Rule out sleep before blaming behavior

55%

EDS or narcolepsy reported

Looks like behavior

Irritability, a short fuse, outbursts when woken, falling school performance, night foraging

9%

cataplexy diagnosed

Screen every year

Sleep-disordered breathing, EDS, narcolepsy, cataplexy and insomnia

6%

narcolepsy diagnosed

Test the mismatch

Use MSLT when sleepiness is out of proportion to treated OSA

Treat, and watch

Modafinil or pitolisant can improve sleepiness and behavior; monitor for activation

03

Management



Build structure before adding medication



Why the order matters

- Structure, routine and predictability (where possible) are key
- Medication may not help until the stressor is removed
- Every caregiver needs PWS-specific training

Prescribing principles in PWS



Start low, go slow

Side effects are common even at usual starting doses



One change at a time

So you can tell what helped and what harmed



Beware activation

SSRIs and aripiprazole (Abilify) can worsen behavior or unmask psychosis



Limit polypharmacy

Reassess regularly and deprescribe when you can



Consider pharmacogenomics

Especially after several medication failures



Watch physiology

Low water intake, sleepiness, glucose and weight; monitor for side effects

Medication patterns from clinic experience

Class	What we often see	Cautions
SSRIs / anxiolytics	Escitalopram at low doses (e.g., 5 mg) is often well tolerated; buspirone is an alternative	Fluoxetine and sertraline more often activating; may worsen mood or psychosis
Antipsychotics	Risperidone a good first choice for psychosis (starting 0.25 mg)	Aripiprazole often worsens behavior; dose needs can climb; metabolic effects with long use
Mood stabilizers	Lithium for mood, suicidal/homicidal ideation and impulsive aggression; lamotrigine as an option	Monitor sodium, thyroid, tremor and levels
α2-agonists	Guanfacine ER reduced aggression, skin picking and hyperactivity in an RCT (ages 6–35); in clinic, best as an adjunct	Sedation, often more prolonged in PWS; watch for worsened psychosis or aggression
Wake-promoting	Modafinil or pitolisant for daytime sleepiness can improve behavior	Possible activation

Mood stabilizers in PWS: monitor closely

When we use it

- Mood stabilization, including cyclic mood with UPD
- Suicidal or homicidal ideation tied to refractory depression
- Impulsive aggression

Levels of 0.6–0.8 mEq/L were effective in clinic cases of use of Lithium



Sodium

Low water intake predisposes to hypernatremia with Lithium (one case reached 152); oxcarbazepine causes hyponatremia (use of both can prevent side effects)



Levels and glucose

With lithium, levels can drift; one patient fell to 0.3 with hypoglycemia as mood worsened



Thyroid

Lithium: Check thyroid function at baseline and during treatment



Tremor

Lithium: May limit use even when mood response is excellent

Case: when an SSRI activates

27-year-old man · type I deletion · IQ ~50 · never on growth hormone



Presentation

Two weeks after starting fluoxetine 10 mg: more stubbornness and outbursts, refusing to change clothes, rocking, magical thinking. Mother was frightened by his volatility.



Intervention

Fluoxetine weaned off. Risperidone 0.25 mg at night. A morning dose was tried and caused disabling sleepiness.



Outcome

Back to his sweet baseline on risperidone 0.5 mg nightly alone. Symptoms can return during transitions, such as new respite caregivers.

Lesson: activation can look like new psychiatric illness. Remove the likely offender first, then add the smallest effective dose of medication for psychosis (if needed).

Case: when less is more

11-year-old boy · deletion · IQ ~65 · on growth hormone

1

Arrives on four agents

Ziprasidone 60 mg BID, guanfacine 4 mg, aripiprazole 10 mg, quetiapine 150 mg; slurred speech, nearly falling

2

Inpatient wean of all

Psychotic features emerge once the medication burden is lifted

3

Lithium monotherapy

150 mg BID titrated to 300 mg BID; level 0.8 mEq/L; good response

4

Sodium rises to 152

Oxcarbazepine 150 mg BID added; sodium normalizes

“Happier than he has been in a long time.”

Lesson: crisis-driven polypharmacy can mask the true picture. Simplify, then treat what remains.

04

Into adulthood



Transitions are high-risk moments

Watch for



School to adult services



**New caregivers or
respite staff**



Residential placement



Siblings' milestones

Plan ahead

- Train every caregiver in PWS before they start
- Keep routines and picture schedules consistent across settings
- Use ABA or modified trauma-based therapy around big changes
- Write a crisis plan before a crisis
- Know who to call
- Re-check sleep, weight and medications at each transition

Case: a caregiver change destabilizes mood

27-year-old woman · maternal UPD · IQ ~85 · on growth hormone and oral contraceptives



Presentation

Stable for years on lithium 300 mg BID (level 0.8) plus fluoxetine. New primary caregiver at residential school: volatile outbursts, worsening mood, significant suicidal ideation.



Intervention

Ziprasidone 20 mg BID with meals: dramatic early response. Fluoxetine switched to escitalopram 10 mg. Then rising irritability and inability to reason.



Outcome

Ziprasidone weaned. Mood stabilized on lithium plus escitalopram.

Lesson: transitions are predictable triggers. Plan for them, and judge a new agent over weeks, not days.

Important Interventions



Growth hormone

Continue lifelong at an adult dose for lean mass and tone; caution with uncontrolled diabetes or severe obesity



Sex hormones

Estrogen or testosterone for bone health and confidence; yearly DEXA



Sleep-disordered breathing

OSA and obesity hypoventilation drive irritability and cardiac risk



Metabolic

Weight, diabetes, and hypoglycemia that can mimic mood change



Gastrointestinal

Constipation, gastroparesis and reflux (common) cause discomfort that shows up as behavior



Thyroid and orthopedic

Hypothyroidism; scoliosis needs ongoing monitoring

Adrenal insufficiency: what the evidence shows



60%

children, single-dose metyrapone

de Lind van Wijngaarden, 2008



0–29%

other pediatric and adult studies,
depending on the test

Obrynba, 2018 and others



1.2%

adults (1 of 82), ITT or multiple-
dose metyrapone

Rosenberg, 2020

Why concern persists into adulthood

- Hypothalamic dysfunction; unexplained sudden deaths during illness prompted the original studies
- Illness is hidden: high pain threshold, rare vomiting, unstable temperature, late presentation
- Testing is hard to interpret: ACTH and low-dose stimulation tests can mislead
- Starting thyroid hormone or growth hormone can unmask low cortisol reserve
- Daily glucocorticoids can worsen mood, psychosis, appetite and weight, so keep replacement for confirmed deficiency
- Adult care teams may not know the history: send an emergency letter at every handoff

Keep a low threshold to stress-dose hydrocortisone



Recommendation: in PWS, consider stress-dose hydrocortisone early during major physiologic stress. Do not wait for classic signs of adrenal crisis.

When to consider it

- Surgery or general anesthesia
- Serious illness: pneumonia, sepsis, high fever; any vomiting
- Unexplained hypotension, bradycardia, hypoglycemia or low sodium
- Sudden lethargy or change in mental status

How to make it work

- Adult crisis or major surgery: hydrocortisone 100 mg IV, then 200 mg/24 h; children 50 mg/m²
- Use a short course and stop when the stressor resolves
- Give families an emergency letter and plan; review it at every transition of care
- Test (ITT or metyrapone) when suspicion is ongoing

Case: bradycardia masquerading as decline

60-year-old adult with PWS



Presentation

Cognitive and psychomotor slowing that developed gradually over years. Heart rate in the 30s to 40s.



Intervention

Dual-chamber pacemaker with heart rate control.



Outcome

Cognitive and psychomotor slowing improved.

Lesson: slow decline in an older adult with PWS is not always aging or dementia. Check the heart rate and get an ECG.

Slow heart rate in PWS: what to check



Medications

Guanfacine, clonidine, beta-blockers and lithium (sinus node dysfunction)



Hypothyroidism and hypothermia

Check thyroid function and core temperature



Adrenal insufficiency

Watch for bradycardia with low blood pressure, low sodium or low glucose



Sleep apnea and hypoventilation

Nocturnal hypoxia drives bradyarrhythmias



Conduction disease and vagal pauses

Pauses can be triggered by swallowing; consider Holter and cardiology referral



Presentation

Fatigue, syncope, falls, or cognitive and psychomotor slowing

Measure what matters to families

PWS Acuity Scale

Pittsburgh Partnership

105-item Personality Questionnaire across the 6 domains, plus a 55-item neurodevelopmental and medical questionnaire. Captures onset, persistence and interference.

PWS Profile

Dykens et al., 2024

57 items covering rigidity, aggression, repetitive questioning, anxiety, depression and distorted thinking. Validated against the CBCL.

HQ-CT

Hyperphagia Questionnaire for Clinical Trials

Standard primary outcome for hyperphagia trials.

CBCL

Child Behavior Checklist

The general reference scale used to validate PWS-specific tools.

PWS pipeline: hyperphagia and weight

Agent	Mechanism	Stage and status	Key details
Vykat XR (diazoxide choline) Neurocrine (from Soleno)	K-ATP channel opener	FDA approved Mar 2025, age 4+	Aug 2026 clinician statement on edema/fluid overload; 7 deaths reported postmarketing, causality not established. Observational study NCT07450664
Setmelanotide Rhythm	MC4R agonist	Phase 2 (n=18, ages 6–23); Phase 3 planned	6-month BMI –3.1%; 8 of 10 with moderate–severe hyperphagia improved ≥7 points on HQ-CT. Label warns of depression and suicidal ideation
RM-718 Rhythm	MC4R agonist	Phase 1, PWS cohort	26-week open-label arm, up to 20 people with PWS
PBF-999 Palobiofarma	PDE10 inhibitor	Phase 2 complete; Phase 3 planned early 2027	Phase 2 in 32 patients aged 12+; end-of-Phase 2 meetings with FDA and EMA done
BMB-101 / BMB-105 Bright Minds	5-HT2C agonist	Phase 2a (NOVA), adults 18–65	Hyperphagia and behavior; NCT07266324. Next-generation BMB-105 in Phase 1
TNX-2900 Tonix	Intranasal oxytocin + magnesium	Phase 2 planned; enrollment Q1 2027	Ages 8–17; 12-week placebo-controlled, three doses; HQ-CT primary endpoint
Tirzepatide Vanderbilt (investigator-led)	GIP/GLP-1 agonist	Phase 4, recruiting	Ages 18–26 with PWS, hypothalamic or general obesity; weight at 48 weeks; NCT06901245

PWS pipeline: behavior and sleep

Agent	Mechanism	Stage and status	Key details
Pitolisant Harmony Biosciences	H3 inverse agonist	Phase 3 (TEMPO)	Excessive daytime sleepiness; topline expected 2H 2026. Phase 2 suggested benefit for behavior
CSTI-500 ConSynance	Triple reuptake inhibitor (5-HT, NE, DA)	Phase 2a open-label, ages 13–50	First dosed Jun 2026 at Vanderbilt; hyperphagia and behavior exploratory; NCT07348601
Transcutaneous VNS FPWR	Noninvasive vagus nerve stimulation	Phase 3, enrollment complete	Temper outbursts; n=102, ages 10–40; completion 2027; NCT06144645
Cannabidivarin (CBDV) Investigator-led	Cannabinoid	Phase 2, enrollment complete	Behavior; NCT03202303
Guanfacine ER Singh et al.	α 2A agonist	RCT published 2025	Ages 6–35: less aggression, skin picking and hyperactivity vs placebo; mild sedation most common
ARD-101 Aardvark	Bitter taste receptor agonist	Phase 3 HERO terminated Jun 2026	FDA full clinical hold May 2026 after cardiac findings at above-target doses in healthy volunteers
Intranasal carbetocin Acadia	Oxytocin analog	Phase 3 COMPASS missed primary endpoint	Sept 2025; hyperphagia endpoint not met

Key takeaways

- 1 Anxiety drives most PWS behavior, starts by school age, and persists into adulthood
- 2 Psychosis and mood disorders emerge in adolescence; UPD carries the highest risk
- 3 Rule out sleep, medical causes, medication activation and transitions first
- 4 Structure and trained caregivers come before medication
- 5 Start low, go slow, change one thing at a time, and simplify when in doubt
- 6 Keep a low threshold to stress-dose hydrocortisone, and check the heart rate when an adult slows down



Thank you

Questions?

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