TONIX PHARMACEUTICALS

TNX-2900

Prader-Willi Syndrome

NASDAQ: TNXP

Version P06099 September 29, 2025 (Doc 1616)

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Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are “forward-looking statements” as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate” and “intend,” among others. These forward-looking statements are based on Tonix’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; risks related to the failure to successfully launch and commercialize Tonmya and any of our approved products; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2024, as filed with the Securities and Exchange Commission (the “SEC”) on March 18, 2025, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

TNX-2900*: Prader-Willi Syndrome (PWS)
Intranasal Potentiated Oxytocin (OT) with Magnesium

RARE DISEASE PORTFOLIO

PROFILE

Prader-Willi Syndrome is the most common genetic cause of life-threatening childhood obesity

- Rare disease occurring in 1 in 10,000 to 1 in 30,000 births

Symptoms include lack of suckling as infants, poor muscle strength, and constant hunger (hyperphagia) in adolescents and young adults

- In animal models, OT has improved suckling and suppressed hunger
  - Tonix's patented potentiated OT formulation is believed to increase activity of OT at OT receptors (OXTR)

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Treatment of Prader-Willi syndrome in children and adolescents (8-17.5 years). There is an unmet need for well tolerated and effective treatments for PWS.

Additional Indications: Rare Hyperphagia Conditions

Status: Granted Orphan Drug Designation and Rare Pediatric Disease Designation by FDA, received IND clearance for Phase 2 trial from FDA

Next Steps: Initiating a Phase 2 trial in 2026

*TNX-2900 is has not been approved for any indication.

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Prader-Willi Syndrome

Cause	~65% of cases are due to a new deletion on paternal chromosome 15; first genetic imprinting disorder recognized in humans
Prevalence	1 in 10,000 to 1 in 30,000[1,2]; most common syndromic cause of obesity
Symptoms	In infants, severe hypotonia and difficulty sucking. In children and adolescents, delayed global development, decreased growth resulting in short stature, intellectual difficulties, hypogonadism, hyperphagia, life-threatening obesity, behavioral problems
Diagnosis	Genetic testing: DNA methylation
Treatment	No cure, and limited FDA approved treatments available

[1]Angulo MA, et al. *J Endocrinol Invest.* 2015;38(12):1249-1263.
[2]McCandless, Shawn E et al. SUN-604 U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, *Journal of the Endocrine Society*, Volume 4, Issue Supplement_1, April-May 2020, SUN–604, https://doi.org/10.1210/jendso/bvaa046.993

Progression of Prader-Willi Syndrome[1]

YRS: 0 | 1 | 2 | 4 | 8 | 16 | 24 | 32

0 yrs

0 to 9 months

9 to 25 months

2 to 4.5 years

4.5 to 8 years

8 years to adulthood

Adulthood

Phase 0
Low birth weight

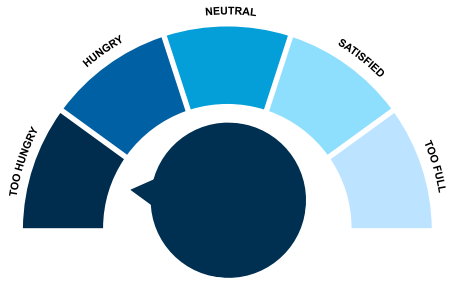
Phase 1a
Failure to thrive, feeding difficulties, hypotonia, increased infant mortality

Phase 1b
Normal growth

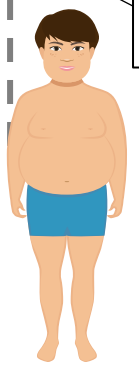
Phase 2a
Weight increase without appetite increase

Phase 2b
Weight and appetite increase; obesity occurs if allowed to eat what they want

Phase 3
Hyperphagia



Average age at death: 22.1 years[2]



Phase 4
Return to normal appetite; this phase is not often reached

RARE DISEASE PORTFOLIO

1. Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.
2. Bellis SA, et al. Eur J Med Genet 2022;65(1)104379.

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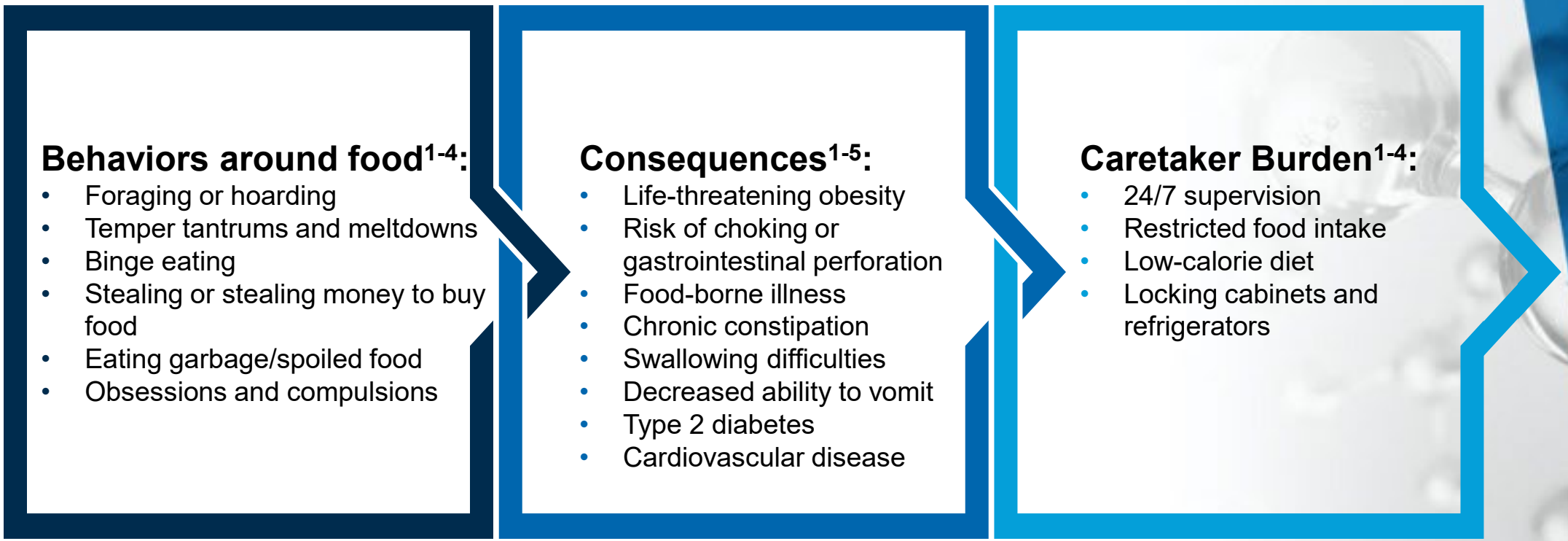
Dangers of PWS Hyperphagia



1. Miller JL, et al. *Am J Med Genet A*. 2011;155A(5):1040-1049.
2. Butler MG, et al. *Genet Med*. 2017;19(6):635-642.
3. Butler MG. NORD. Updated 2018. Accessed May 25, 2022. https://rarediseases.org/rare-diseases/prader-willi-syndrome/
4. Prader-Willi Syndrome Association USA. Accessed May 25, 2022. https://www.pwsausa.org/what-is-prader-willi-syndrome/
5. Muscogiuri G, et al. *J Endocrinol Invest*. 2021;44(10):2057-2070.

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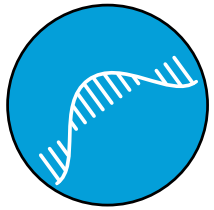
Abnormalities of the Oxytocin System in Patients with PWS

PWS patients have

Increased oxytocin in blood plasma[1,2]



Decreased oxytocin mRNA[1]

Low levels of oxytocin receptor expression[2]

Decreased or abnormal oxytocin neurons (especially in the PVN)[1]

PVN=paraventricular nucleus.

1. Correa-da-Silva F, et al. *J Neuroendocrinol.* 2021;33(7):e12994.
2. Jurek B, et al. *Physiol Rev.* 2018;98(3):1805-1908.

History of Oxytocin Use

Synthetic oxytocin has been used to induce labor for over 65 years[1]

Due to the role of endogenous oxytocin in pain regulation and social behavior, the administration of exogenous oxytocin has been studied in a wide variety of therapeutic areas[2]

Intravenous administration of oxytocin has been met with many challenges:

- Short half-life:
  - Intravenous oxytocin has a half-life of roughly 3-5 minutes[3]
- Difficulty crossing the blood-brain barrier from peripheral circulation[4]

RARE DISEASE PORTFOLIO

[1] den Hertog CE, et al. *Eur J Obstet Gynecol Reprod Biol.* 2001;94(1):8-12.
[2] Bakermans-Kranenburg MJ, et al. *Transl Psychiatry.* 2013;3(5):e258.
[3] Oxytocin. Package insert. Hikma Pharmaceuticals USA Inc.; 2011.
[4] Quintana DS, et al. *Mol Psychiatry.* 2021;26(1):80-91.

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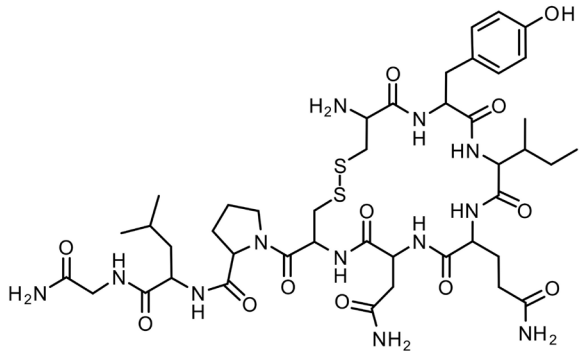
Functions of Natural and Therapeutic Oxytocin



Childbirth[1-3]:

Natural

- Stimulates uterine contractions during childbirth

Therapeutic

- Widely used for the induction of labor in an estimated 25% of women in Western countries

Breastfeeding[1,4,5]:

Natural

- Oxytocin is responsible for the let-down reflex
- Contracts the muscles around the glands that produce milk

Therapeutic

- Approved to stimulate milk production, but discontinued in the US

Behavioral regulation[1,6]:

Natural

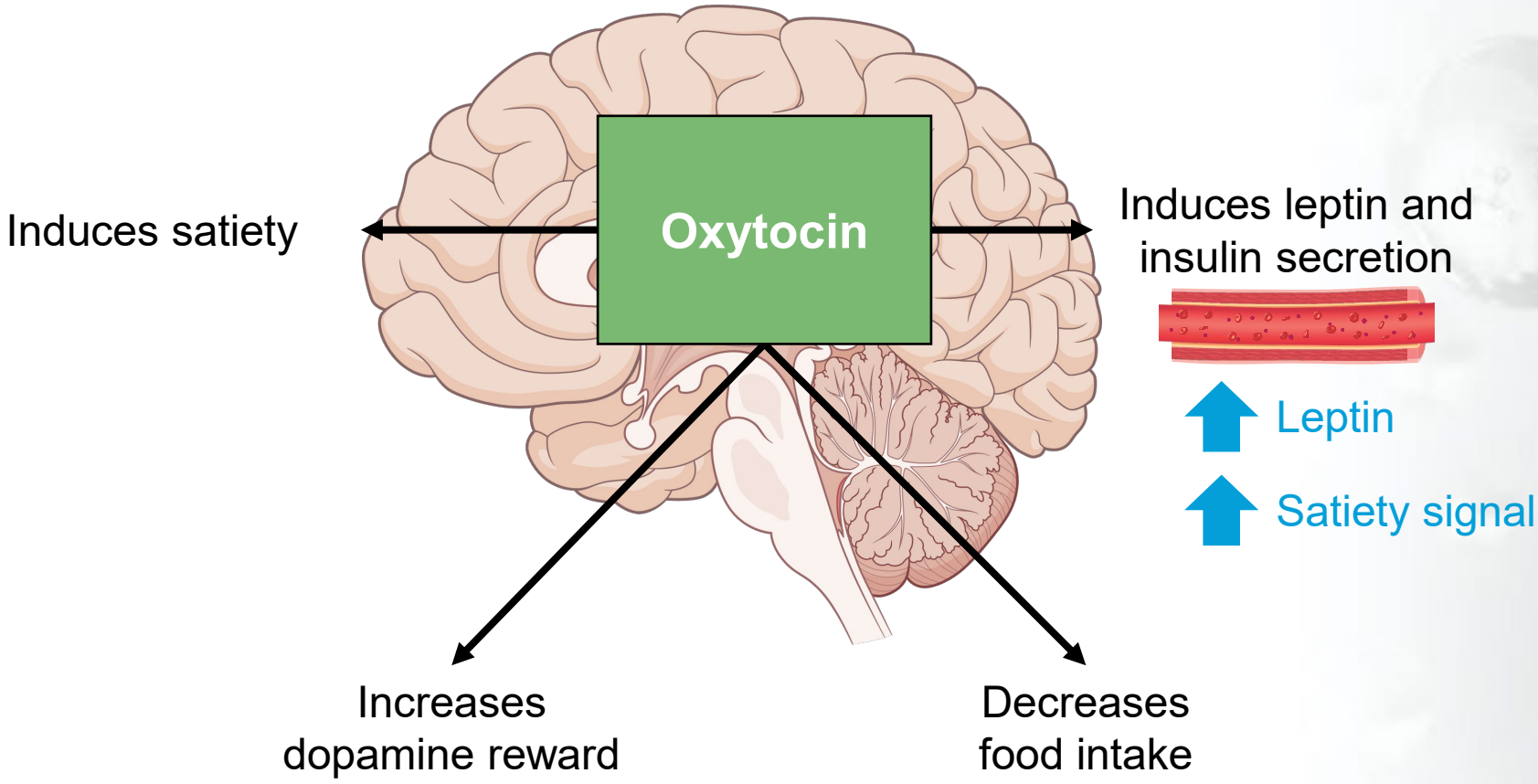
- Oxytocin plays a role in prosocial behaviors and bonding
- Signals satiety and suppresses appetite

Therapeutic

- No approved oxytocin therapy

1. McCormack SE, et al. *Endocr Rev*. 2020;41(2):121-145.
2. Kuwabara Y, et al. *Arch Gynecol Obstet*. 1987;241(1):13-23.
3. Boie S, et al. *Cochrane Database Syst Rev*. 2018;8(8):CD012274.
4. World Health Organization. World Health Organization; 2009. https://www.ncbi.nlm.nih.gov/books/NBK148970/
5. MPR. December 12, 2013. Accessed June 23, 2022. https://www.empr.com/home/news/retrophin-to-reintroduce-syntocinon-nasal-spray/
6. Bartz JA, et al. *Trends Cogn Sci*. 2011;15(7):301-309.

Oxytocin Plays Major Role in Satiety[1-3]



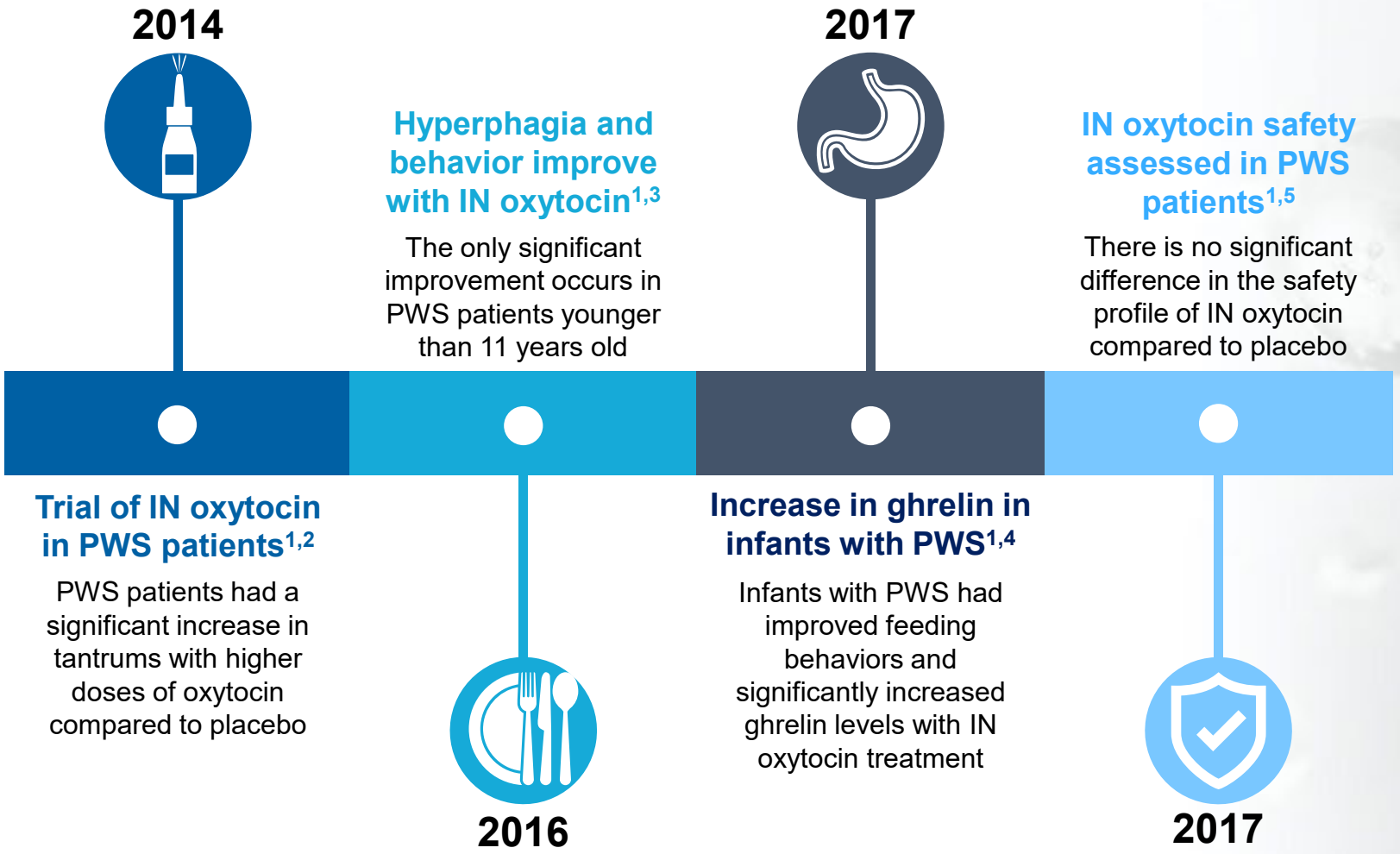
1. Correa-da-Silva F, et al. *J Neuroendocrinol.* 2021;33(7):e12994.
2. McCormack SE, et al. *Endocr Rev.* 2020;41(2):121-145.
3. Kerem L, et al. *Int J Mol Sci.* 2021;22(14):7737.

Intranasal Use of Oxytocin

- Intranasal oxytocin was introduced as a lactation aid in the early 1960s[1]
- Numerous studies have investigated chronic and acute intranasal oxytocin for the treatment of neuropsychiatric disorders and pain[2]
  - Intranasal oxytocin has been studied in anxiety disorders,[3] autism,[4] PTSD,[5] schizophrenia,[6] and pain[7]
- Chronically administered intranasal oxytocin is generally very well tolerated[8-11]
- Intranasal oxytocin has been found to be generally safe and well tolerated in a variety of healthy populations ranging from infancy to old age[12,13]

1. Skarsten KW. *Tidsskr Nor Laegeforen*. 1962;82:8-10.
2. Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
3. Jones C, et al. *Dialogues Clin Neurosci*. 2017;19(2):193-201.
4. Guastella AJ, et al. *Biol Psychiatry*. 2010;67(7):692-694.
5. Pitman RK, et al. *Psychiatry Res*. 1993;48(2):107-117.
6. Feifel D, et al. *Biol Psychiatry*. 2016;79(3):222-233.
7. Boll S, et al. *Neuroscience*. 2018;387:149-161.
8. Rung, JM, et al. *Psychopharmacology (Berl)*. 2021;1-14.
9. Horta M, et al. *Neurosci Biobehav Rev*. 2020;108:1-23.
10. Finger E, et al. *Neurology*. 2015;84(2):174-181.
11. Barraza JA, et al. *Exp Clin Psychopharmacol*. 2013;21(2):85-92.
12. DeMayo MM, et al. *Drugs*. 2017;19(5):391-410.
13. Verhees MWFT, et al. *Psychopharmacology (Berl)*. 2018;235(8):2471-2477.

Intranasal (IN) Oxytocin As PWS Treatment



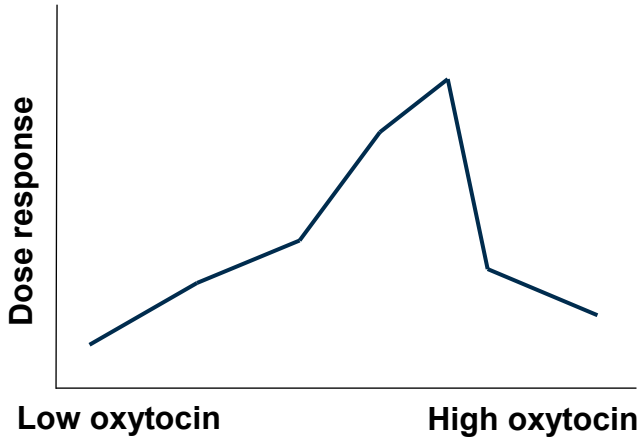
Despite strong evidence for the role of OT in satiety, there are challenges in using OT for the treatment of PWS

1. McCormack SE, et al. *Endocr Rev*. 2020;41(2):121-145.
2. Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
3. Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.
4. Tauber M, et al. *Pediatrics*. 2017;139(2):e20162976.
5. Miller JL, et al. *Am J Med Genet A*. 2017;173(5):1243-1250.

Challenges in Intranasal Oxytocin Studies in PWS

- No significant difference with IN oxytocin treatment but significantly increased tantrums at higher doses[4]
- Significant improvement in hyperphagia but only in patients younger than 11 years old[5]

- Central oxytocin levels are difficult to measure[1]
- Dose response is not linear but an inverted-U shape[1,2]

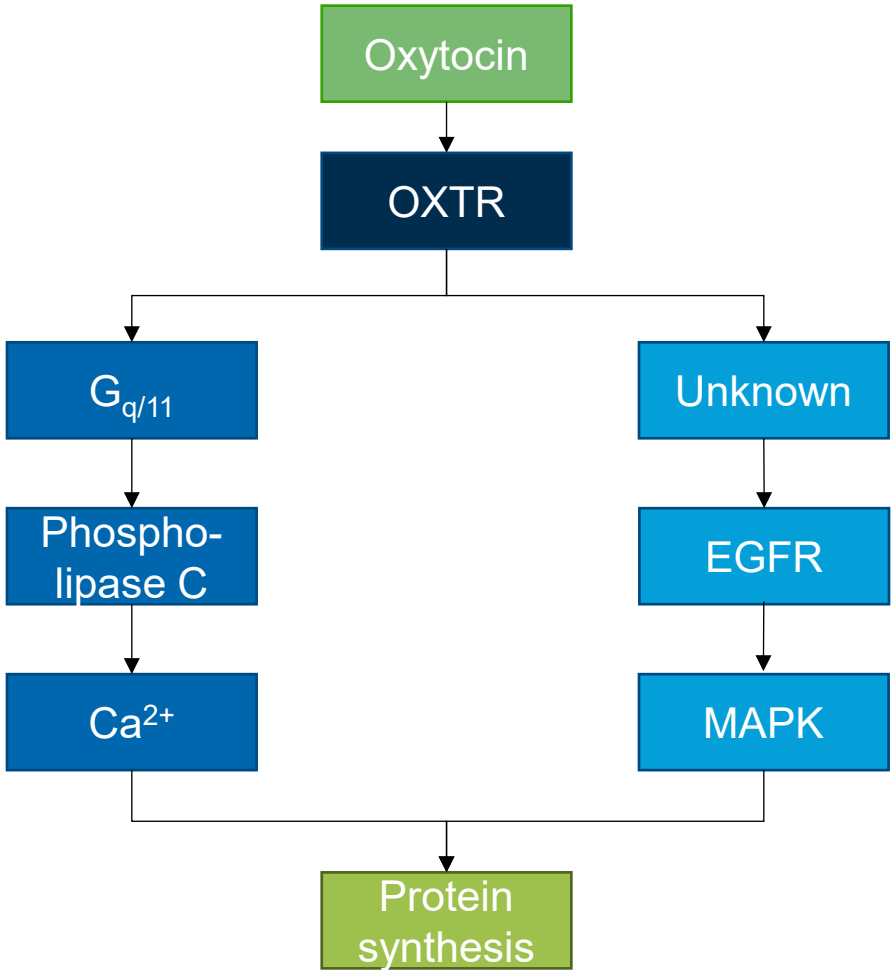


- Recent nonclinical reports show that magnesium is needed for full oxytocin receptor binding[2,3]
- Magnesium enables a full dose response[2,3]

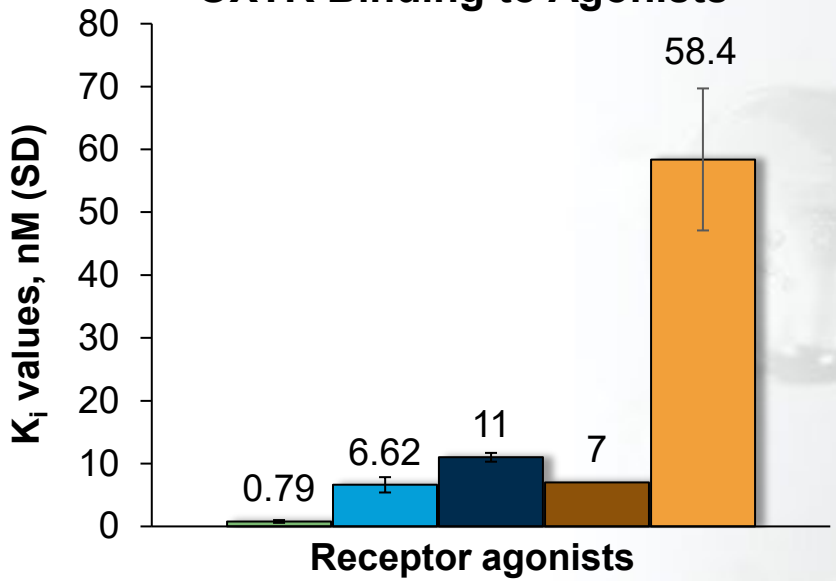
1. Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
2. Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.
3. Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.
4. Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
5. Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.

Oxytocin Receptor (OXTR)

OXTR Signaling Cascade



OXTR Binding to Agonists[1]



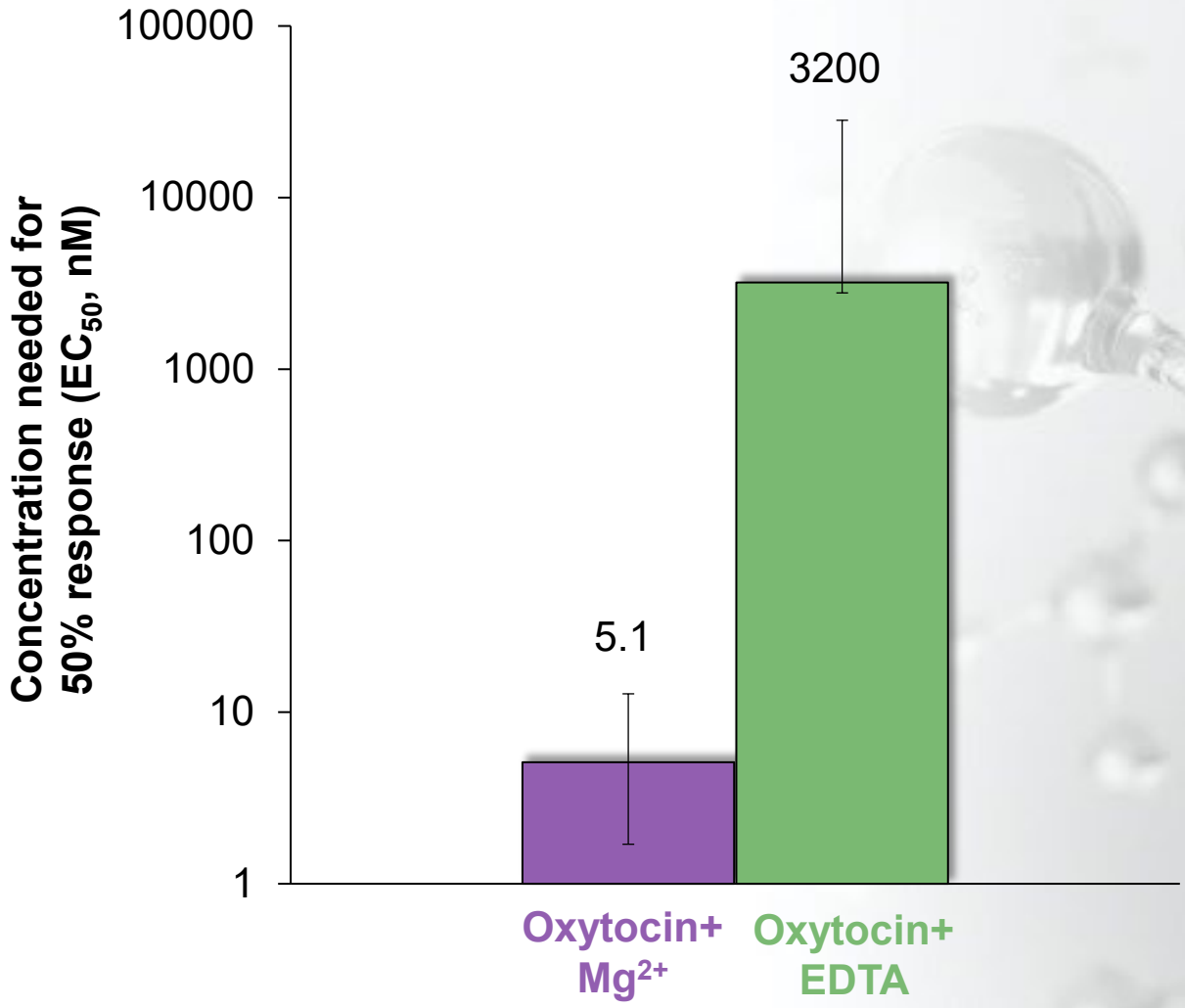
- **Oxytocin**
- **TGOT** = highly selective agonist
- **Atosiban** = functionally selective agonist (can act as an antagonist depending on the G-protein coupled to OXTR)
- **Carbetocin** = oxytocin analog – weak agonist with mixed antagonist activity[2]
- **WAY 267,464** = nonpeptide agonist more specific for the vasopressin receptor

EGFR=epidermal growth factor receptor; MAPK=mitogen activated protein kinase; OXTR=oxytocin receptor

[1] Jurek B, et al. *Physiol Rev*. 2018;98(3):1805-1908.
[2] Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.

Oxytocin+Mg^{2+} Activates OXTR Secondary Messengers

Magnesium is needed not only for oxytocin binding to OXTR but also for OXTR activation



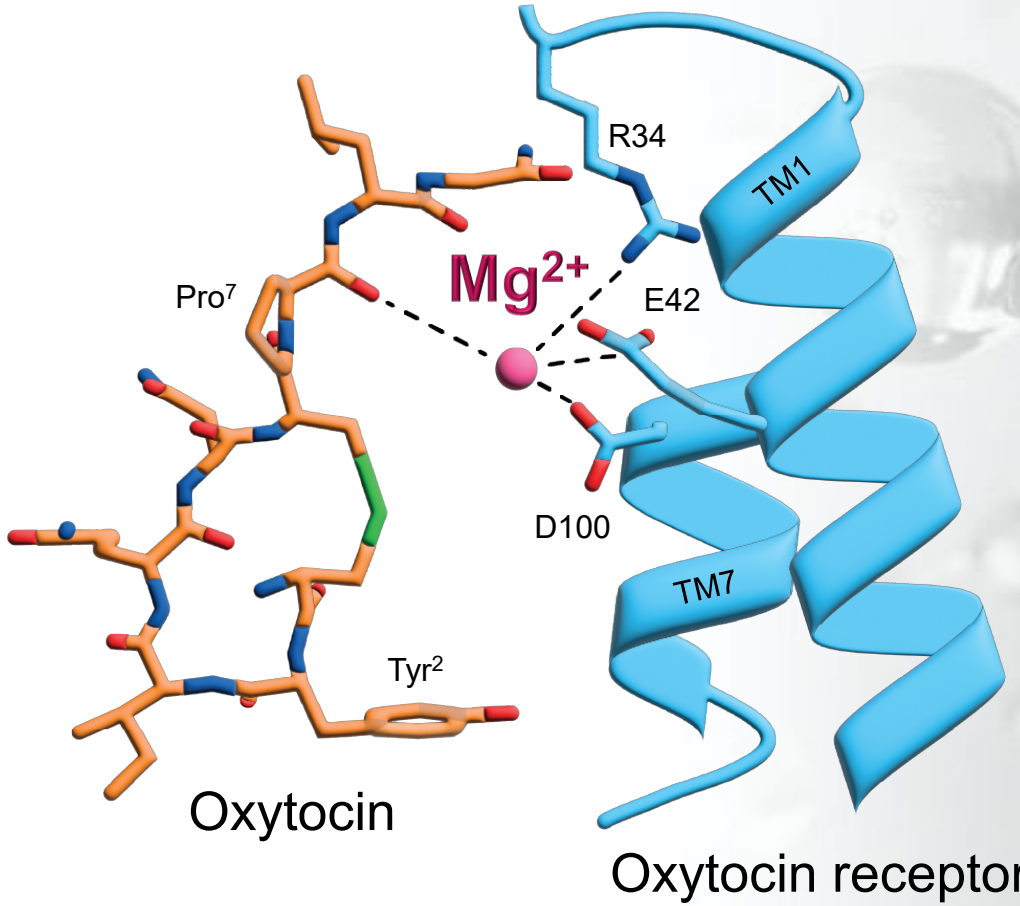
BRET assay in HEK-293 cells

BRET=bioluminescence resonance energy transfer; EDTA=etheylenediaminetetraacetic acid; HEK=human embryonic kidney; OXTR=oxytocin receptor.

Meyerowitz JG, et al. *Nat Struct Mol Biol.* 2022;29(3):274-281.

Oxytocin Requires Magnesium for Receptor Binding

- OXTR exists in 2 conformational states[1]:
  - Low affinity
  - High affinity
- Magnesium ions are necessary for the high-affinity state[1,2]
- Without magnesium ions present, oxytocin cannot achieve full binding to OXTR[2]



OXTR=oxytocin receptor.

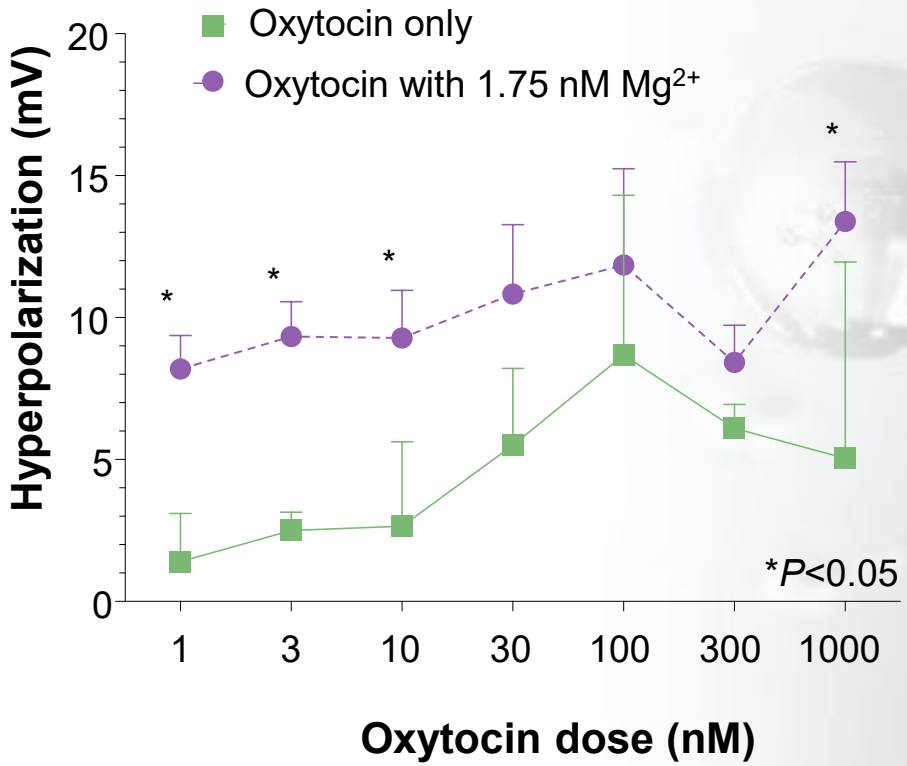
1. Jurek B, et al. *Physiol Rev*. 2018;98(3):1805-1908.
2. Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.

Phase 2 study to investigate TNX-2900 for the treatment of hyperphagia in PWS

- FDA has cleared the IND for a Phase 2 randomized, double-blind, placebo-controlled, parallel design study to evaluate the safety, tolerability, and efficacy of TNX-2900 in PWS
- Key elements of study design:
  - Male and female participants with PWS, ages 8 to 17.5 years.
  - Eligible participants will be randomized to receive TNX-2900 at 1 of 3 dose levels, or placebo, with a ratio of 1:1:1:1.
  - Treatment duration of 12 weeks.
  - The primary efficacy endpoint will be the change in score in the validated Hyperphagia Questionnaire for Clinical Trials (HQ-CT).
- Anticipated start date of 2026

Addition of Mg^{2+} Potentially Expands the *in vivo* Useful Dose Range of Intranasal Oxytocin in Animals

- A nonlinear dose response has been demonstrated in the use of intranasal oxytocin
- This decreases efficacy at higher doses
- Addition of Mg^{2+} rescues the efficacy of oxytocin at high doses



In vitro whole-cell voltage-clamp recordings of rat trigeminal nerves exposed to oxytocin solution with and without additional magnesium ions

Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.

Highlights

- Hyperphagia in Prader-Willi syndrome (PWS) is severe and life-threatening.
- There is a high unmet need for safe and effective treatments for PWS.
- Oxytocin is one of the hormones responsible for signaling satiety.
- The oxytocin receptor requires magnesium ions for the high-affinity conformation for signaling satiety.
- TNX-2900* combines oxytocin with magnesium for improved receptor binding and potentially improved therapeutic action.
- An Investigational New Drug (IND) application has been cleared for a Phase 2 study to test the efficacy and safety of TNX-2900 in the treatment of PWS.
- Tonix is initiating a Phase 2 trial for TNX-2900 in PWS in 2026.

*TNX-2900 is an investigational drug and has not been approved for any indication

THANK YOU