UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): March 23, 2023

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On March 23, 2023, Tonix Pharmaceuticals Holding Corp. (the "Company") announced that Herbert Harris, M.D., Ph.D., the Company's Executive Vice President, Translational Medicine, delivered an oral presentation on March 23, 2023, at the Rare Disease Innovation and Partnership Summit (the "Presentation"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. The Presentation, which may contain nonpublic information, is filed as Exhibit 99.02 hereto and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01 and 99.02 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On March 23, 2023, the Company announced that Dr. Harris presented data from the Presentation, entitled "*TNX-2900 (Intranasal Potentiated Oxytocin) in Development for the Treatment of Hyperphagia in Adolescents and Young Adults with Prader-Willi Syndrome*," which includes data showing the enhancing effects of magnesium (Mg^{2+}) on the activation of oxytocin receptors. The Mg^{2+} enhanced formulation of intranasal oxytocin is the basis for the Company's TNX-2900 product candidate, in development to treat hyperphagia in adolescent and young adult patients with Prader-Willi syndrome, and for the Company's TNX-1900 product candidate in development to prevent migraine headaches in chronic migraineurs.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, “expect,” “anticipate,” “intend,” “plan,” “believe,” “estimate,” “potential,” “predict,” “project,” “should,” “would” and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company’s filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description
99.01	Press release of the Company, dated March 23, 2023
99.02	TNX-2900 (Intranasal Potentiated Oxytocin) in Development for the Treatment of Hyperphagia in Adolescents and Young Adults with Prader-Willi Syndrome
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: March 23, 2023

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99-01

Tonix Pharmaceuticals Presents Non-Clinical Data on TNX-2900 for the Potential Treatment of Hyperphagia in Adolescents and Young Adults with Prader-Willi Syndrome at the Rare Disease Innovation and Partnership Summit

CHATHAM, N.J., March 23, 2023 (GLOBE NEWSWIRE) onix Pharmaceuticals Holding Corp. (Nasdaq: TNXP,)a clinical-stage biopharmaceutical company, today announced that Herbert Harris, M.D., Ph.D., Executive Vice President, Translational Medicine of Tonix Pharmaceuticals, delivered an oral presentation on March 23, 2023, at the Rare Disease Innovation and Partnership Summit being held as a hybrid event in Philadelphia, Pa. A copy of the presentation is available under the Scientific Presentations tab of the Tonix website atwww.tonixpharma.com. Additional information can be found on the Rare Disease Innovation and Partnership Summit website here.

The oral presentation, titled, *"TNX-2900 (Intranasal Potentiated Oxytocin) in Development for the Treatment of Hyperphagia in Adolescents and Young Adults with Prader-Willi Syndrome,"* includes data showing the enhancing effects of magnesium (Mg^{2+}) on the activation of oxytocin receptors. The Mg^{2+} enhanced formulation of intranasal oxytocin is the basis for TNX-2900, in development to treat hyperphagia, or pathological over-eating, in adolescent and young adult patients with Prader-Willi syndrome (PWS), and for TNX-1900 in development to prevent migraine headaches in chronic migraineurs. TNX-2900 has been granted Orphan Drug designation from the U.S. Food and Drug Administration for the treatment of PWS. There is no treatment currently approved for PWS-related hyperphagia.

"PWS is a rare genetic disorder characterized by failure to thrive in infancy, but leads to hyperphagia in childhood, resulting in PWS being the most common genetic syndromic cause of obesity," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "Tonix is excited to develop TNX-2900, a Mg^{2+}-enhanced formulation of intranasal oxytocin, as a treatment for hyperphagia in adolescents and young adults with this rare disease."

"Hyperphagia is more than just insatiable appetite. It leads to extreme behavioral and metabolic effects. Consequences around this abnormal food behavior can be life-threatening, particularly obesity and cardiovascular disease, the latter of which is a leading cause of death in people with PWS," said Dr. Harris. "Oxytocin is an anorexigenic hormone that reduces appetite and signals fullness. 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."

Tonix licensed the technology to treat PWS from Inserm Transfert, the private subsidiary of Inserm (the French National Institute of Health and Medical Research). In addition, Tonix has entered into a sponsored research agreement with Aix-Marseille Université to study oxytocin in the genetically engineered mouse model of PWS. In adults, hyperphagia in Prader-Willi can lead to obesity and other complications associated with significant mortality. In newborns, PWS causes a deficiency in suckling, which has been shown to be normalized by oxytocin treatment.

About Prader-Willi Syndrome

Prader-Willi syndrome is recognized as the most common genetic cause of life-threatening childhood obesity[1] and affects males and females with equal frequency and all races and ethnicities. The hallmarks of Prader-Willi syndrome are lack of suckling in infants and, in children and adults, severe hyperphagia, an overriding physiological drive to eat, leading to severe obesity and other complications associated with significant mortality. There is currently no approved treatment for either the suckling deficit in babies or the obesity and hyperphagia in older children associated with Prader-Willi syndrome.

[1]Foundation for Prader-Willi Research (fpwr.org).

About TNX-2900 and Tonix's Potentiated Oxytocin Platform

TNX-2900 is based on Tonix's patented intranasal potentiated oxytocin formulation intended for use by adults and adolescents. Tonix's patented potentiated oxytocin formulation is believed to increase specificity for oxytocin receptors relative to vasopressin receptors as well as to enhance the potency of oxytocin. Tonix is also developing a different intranasal formulation and device, designated TNX-1900, for prophylaxis of chronic migraine and for the treatment of insulin resistance and related conditions. Oxytocin is a naturally occurring human hormone that acts as a neurotransmitter in the brain. It was originally approved by the U.S. Food and Drug Administration as Pitocin®*, an intravenous infusion or intramuscular injection drug, for use in pregnant women to induce labor. An intranasal form of oxytocin was marketed in the U.S. by Novartis to assist in the production of breast milk as Syntocinon®** (oxytocin nasal 40 units/ml), but the product was discontinued, and the New Drug Application was withdrawn.

**Pitocin® is a trademark of Par Pharmaceutical, Inc.*

***Syntocinon® is a trademark of BGP Products Operations GmbH.*

Tonix Pharmaceuticals Holding Corp.*

Tonix is a clinical-stage biopharmaceutical company focused on discovering, licensing, acquiring and developing therapeutics to treat and prevent

human disease and alleviate suffering. Tonix's portfolio is composed of central nervous system (CNS), rare disease, immunology and infectious disease product candidates. Tonix's CNS portfolio includes both small molecules and biologics to treat pain, neurologic, psychiatric and addiction conditions. Tonix's lead CNS candidate, TNX-102 SL (cyclobenzaprine HCl sublingual tablet), is in mid-Phase 3 development for the management of fibromyalgia with interim data expected in the second quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition, for which a Phase 2 study was initiated in the third quarter of 2022. TNX-1900 (intranasal potentiated oxytocin), a small molecule in development for chronic migraine, is currently enrolling with interim data expected in the fourth quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets), a once-daily formulation of tianeptine being developed as a treatment for major depressive disorder (MDD), is also currently enrolling with interim data expected in the fourth quarter of 2023. TNX-1300 (cocaine esterase) is a biologic designed to treat cocaine intoxication and has been granted Breakthrough Therapy designation by the FDA. A Phase 2 study of TNX-1300 is expected to be initiated in the second quarter of 2023. Tonix's rare disease portfolio includes TNX-2900 (intranasal potentiated oxytocin) for the treatment of Prader-Willi syndrome. TNX-2900 has been granted Orphan Drug designation by the FDA. Tonix's immunology portfolio includes biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft and xenograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the second quarter of 2023. Tonix's infectious disease pipeline includes TNX-801, a vaccine in development to prevent smallpox and mpox, for which a Phase 1 study is expected to be initiated in the second half of 2023. TNX-801 also serves as the live virus vaccine platform or recombinant pox vaccine platform for other infectious diseases. The infectious disease portfolio also includes TNX-3900, a class of broad-spectrum small molecule oral antivirals.

**All of Tonix's product candidates are investigational new drugs or biologics and have not been approved for any indication.*

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of 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," "expect," 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, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; 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. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, and periodic 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. The information set forth herein speaks only as of the date thereof.

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Exhibit 99-02

Cautionary Note on Forward-Looking Statements

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; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; 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, 2022, as filed with the Securities and Exchange Commission (the "SEC") on March 13, 2023, 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.

RARE DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

TNX-2900*: Hyperphagia in Prader-Willi Syndrome
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

Differentiator: No approved therapeutic currently on the market for hyperphagia in PWS

Dangers of PWS Hyperphagia:

DEVELOPMENT PROGRAM

Market Entry: Hyperphagia in Prader-Willi Syndrome

Additional Indications: Rare Hyperphagia Conditions

Status: Phase 2 ready

Next Steps: IND submission

Patents Issued

*TNX-2900 is in the pre-IND stage of development and has not been approved for any indication.

[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.

TONIX PHARMACEUTICALS

TNX-2900*: Prader-Willi Syndrome
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)

DEVELOPMENT PROGRAM

Market Entry: Hyperphagia in Prader-Willi Syndrome

Additional Indications: Rare Hyperphagia Conditions

Status: Phase 2 ready

Next Steps: IND submission

Patents Issued

*TNX-2900 is in the pre-IND stage of development and has not been approved for any indication.

TONIX PHARMACEUTICALS

Prader-Willi Syndrome (PWS)

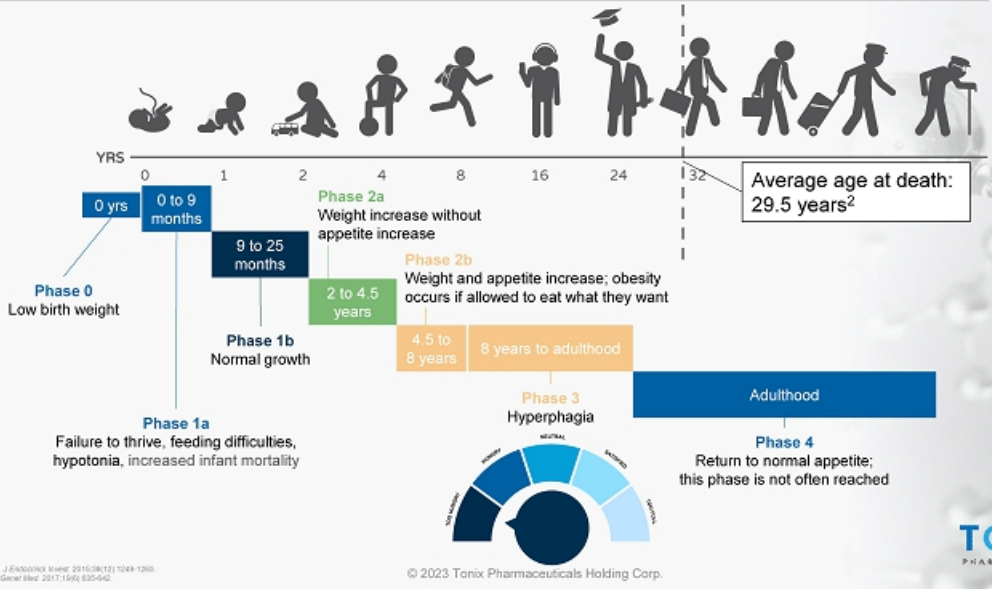
Cause	~65% of cases are due to a new deletion on paternal chromosome 15; first genetic imprinting disorder recognized in humans
Prevalence	1 in 10,000 to 1 in 30,000[1,2]; most common syndromic cause of obesity
Symptoms	In infants, severe hypotonia and difficulty sucking. In children and adolescents, 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, but human growth hormone treatment is FDA approved for growth failure in PWS children

[1]Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.
[2]McCandless, Shawni E et al. SUN-664 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–664, https://doi.org/10.1210/jendso/bvaa046.083

RARE DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

Progression of Prader-Willi Syndrome[1]



[1] Angulo MA, et al. *J Endocrinol Invest*. 2015;38(12):1249-1263.
[2] Butler MG, et al. *Genet Med*. 2017;19(6):635-642.

RARE DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

Dangers of PWS Hyperphagia

Behaviors around food[1-4]:
- Foraging or hoarding
- Temper tantrums and meltdowns
- Binge eating
- Stealing or stealing money to buy food
- Eating garbage/spoiled food
- Obsessions and compulsions

Consequences[1-5]:
- Life-threatening obesity
- Risk of choking or gastrointestinal perforation
- Food-borne illness
- Chronic constipation
- Swallowing difficulties
- Decreased ability to vomit
- Type 2 diabetes
- Cardiovascular disease

Caretaker Burden[1-4]:
- 24/7 supervision
- Restricted food intake
- Low-calorie diet
- Locking cabinets and refrigerators

There is no treatment for PWS-related hyperphagia[4]

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):2057-2073.

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 application of oxytocin has been met with many challenges:

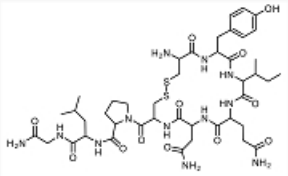
- Short half-life:
  - Intravenous oxytocin has a half-life of roughly 3 minutes[3]
- Difficulty crossing the blood-brain barrier[4]

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.

TONIX PHARMACEUTICALS

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

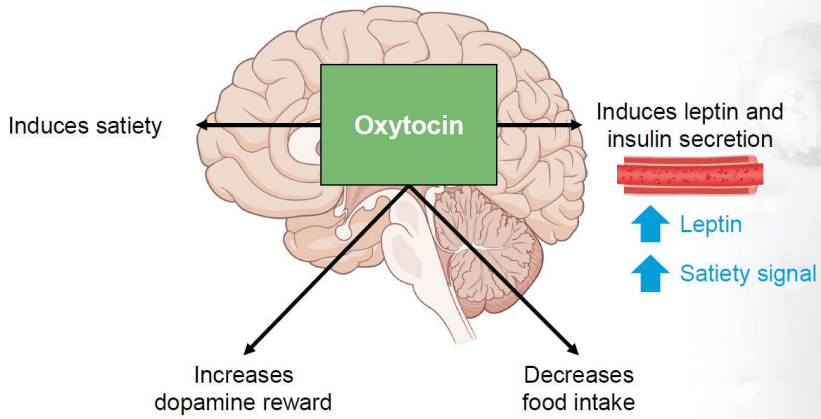
- No approved oxytocin therapy

RARE DISEASE PORTFOLIO

[1] McCormack SE, et al. *Endocr Rev*. 2020;41(2):121-145.
[2] Kuwabara Y, et al. *Arch Gynecol Obstet*. 1997;241(1):15-23.
[3] Bowe S, et al. Cochrane Database Syst Rev. 2015;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/letrophin-to-reintroduce-syntocinon-nasal-spray/
[6] Bartz JA, et al. *Trends Cogn Sci*. 2011;15(7):301-309.

TONIX PHARMACEUTICALS

Oxytocin Plays Major Role in Satiety[1-3]



RARE DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

[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

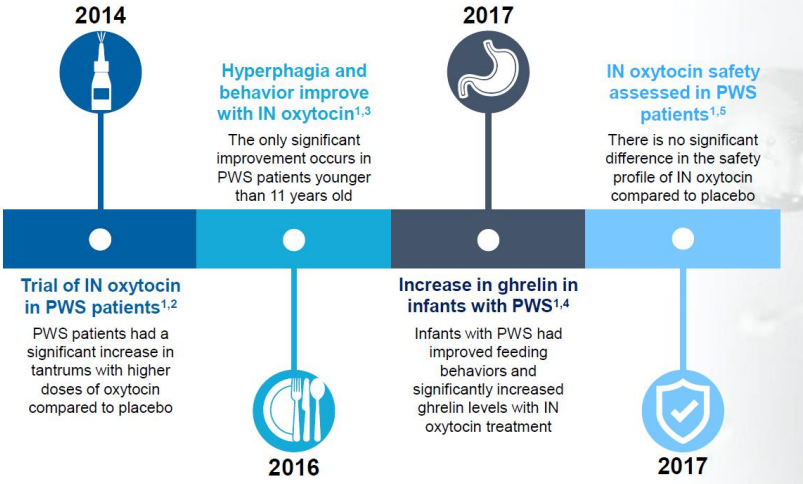
- Intranasal oxytocin was introduced as a lactation aid in the early 1960s[1]
- Numerous studies have investigated chronic and acute intranasal oxytocin for the treatment of neuropsychiatric disorders and pain[2]
  - Intranasal oxytocin has been studied in anxiety disorders,[3] autism,[4] PTSD,[5] schizophrenia,[6] 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]

RARE DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

[1] Skarstein 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*. 2009;73(9):222-233.
[7] Boll S, et al. *Neuroscience*. 2016;387:149-161.
[8] Rung JM, et al. *Psychopharmacology (Berl)*. 2021;1-14.
[9] Hoda M, et al. *Neurosci Biobehav Rev*. 2020;108:1-23.
[10] Finger S, 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):391-413.
[13] Verbeke WMPT, et al. *Psychopharmacology (Berl)*. 2018;235(6):2471-2477.

Intranasal (IN) Oxytocin As PWS Treatment



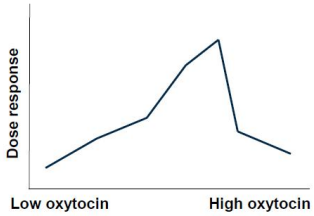
Despite strong evidence for the role of OT in satiety, there are challenges in using OT for the treatment of PWS

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 in humans[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 in animals is not linear but an inverted-U shape[1,2]

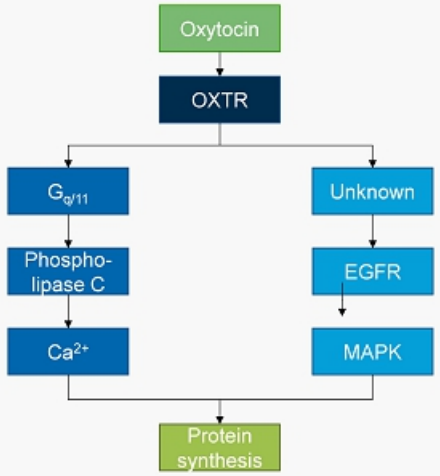


- Recent reports in animals show that magnesium is needed for full oxytocin receptor binding[2,3]
- Magnesium enables a full dose response[2,3]

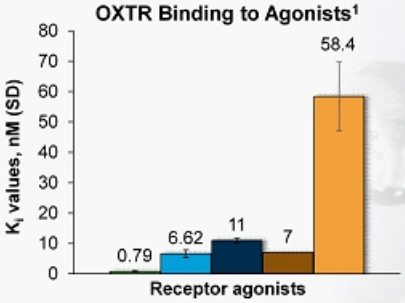
1. Quintana DS, et al. *Mol Psychiatry*. 2021;26(1):80-91.
2. Bharadwaj VN, et al. *Pharmaceutics*. 2022;14(5):1105.
3. Meyerowitz JG, et al. *Nat Struct Mol Biol*. 2022;29(3):274-281.
4. Einfeld SL, et al. *Am J Med Genet A*. 2014;164A(9):2232-2239.
5. Kuppens RJ, et al. *Clin Endocrinol (Oxf)*. 2016;85(6):979-987.

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.

RARE DISEASE PORTFOLIO

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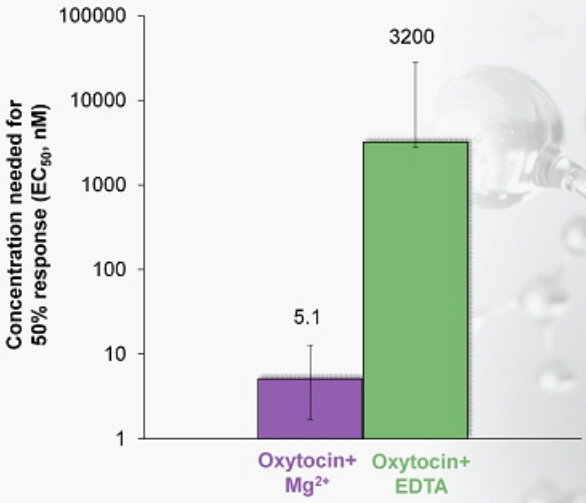
Oxytocin+Mg^{2+} Activates OXTR Secondary Messengers

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.

RARE DISEASE PORTFOLIO

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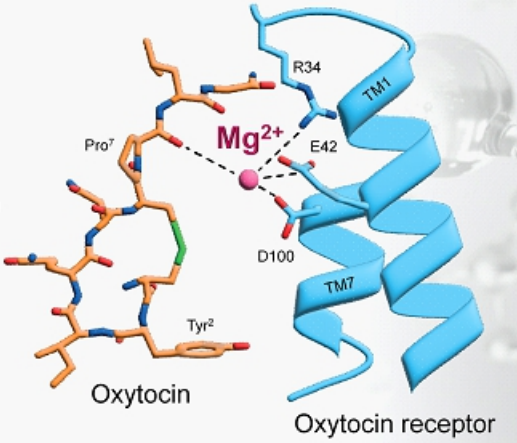
Oxytocin Requires Magnesium for Receptor Binding

- 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]



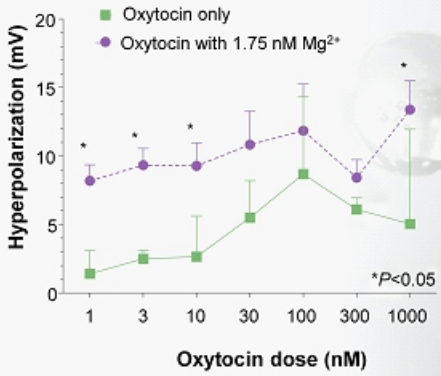
OXTR=oxytocin receptor.

[1] Jurek B, et al. Physiol Rev. 2019;99(3):1805-1868.
[2] Meyerowitz JG, et al. Nat Struct Mol Biol. 2022;29(3):274-281.

TONIX PHARMACEUTICALS

Addition of Mg^{2+} 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

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

TONIX PHARMACEUTICALS

Highlights

- Hyperphagia in Prader-Willi syndrome (PWS) is severe and life-threatening
  - There is currently no treatment for hyperphagia in adolescents and young adults with 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
- TNX-2900 is in development to treat hyperphagia in adolescents and young adults with PWS

*TNX-2900 is an investigational drug in the pre-IND stage of development and has not been approved for any indication

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