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): May 17, 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 May 17, 2023, Tonix Pharmaceuticals Holding Corp. (the "Company") announced the molecular mechanism of action of tianeptine, the active ingredient of the Company's TNX-601 ER (tianeptine hemioxalate extended-release tablets) product candidate, currently in Phase 2 clinical development for the treatment of major depressive disorder ("MDD"). A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference.

The Company updated its TNX-601 presentation, which it intends to place on its website and which may contain nonpublic information. A copy of the presentation 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 May 17, 2023, the Company announced the molecular mechanism of action of tianeptine, the active ingredient of TNX-601 ER, currently in Phase 2 clinical development for the treatment of MDD. Based on pharmacology and medicinal chemistry experiments, scientists at the Company have established that tianeptine is an agonist for the nuclear peroxisome proliferator-activated receptor ("PPAR") isoforms PPAR-β/δ and PPAR-γ, and tianeptine's effects on these PPAR isoforms account for its ability to induce neuroplasticity in cultured neurons. The findings upset a long-held belief that the only way to restore the connectivity of neurons damaged in the state of depression was to increase the synaptic levels or activity of neurotransmitters such as the monoamines serotonin, norepinephrine, and dopamine. The new findings show that selective activation of nuclear PPAR-β/δ and PPAR-γ in neurons and supporting glia appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity, or neuroplasticity. Drugs that restore neuroplasticity are called plastogens. Consequently, tianeptine is a plastogen that acts directly on nuclear receptors that regulate gene expression in neurons and microglia.

The new research provides clarity on why tianeptine does not cause sexual dysfunction, weight gain, or several other treatment-limiting toxicities associated with traditional antidepressants. Tianeptine treats depression by activating select nuclear PPAR isoforms, and has little to do with monoaminergic neurotransmitters, which are known to be implicated in the most frequently cited side effects of most marketed antidepressants. Key experiments were performed by scientists at the Company's Research

and Development Center in Frederick, Maryland.

In animal models, tianeptine restores neuroplasticity and reverses stress-induced impairments through activation of select nuclear PPAR isoforms without modulating synaptic monoamine neurotransmitters, mimicking naturally occurring polyunsaturated fatty acid in binding to PPARs.

The Company believes that the proposed mechanism is consistent with the clinical effects of tianeptine in promoting cognition in Alzheimer's disease, Parkinson's disease and bipolar disorder, and is considering the development TNX-601 ER as a treatment for these and other conditions.

The new findings about tianeptine's mechanism dispel the notion that tianeptine's weak μ-opioid receptor activity was central to its mechanism of treating depression and indicate that there is no connection between tianeptine's neuroplastic effects on cultured neurons and its weak μ-opioid receptor agonism. The Company has identified a new chemical entity related to tianeptine, TNX-4300, that restores neuroplasticity in cultured neurons and is free from μ-opioid receptor activity. The Company intends to submit data supporting tianeptine's mechanism of action for presentation at upcoming scientific conferences and for publication in peer reviewed journals.

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 May 17, 2023
99.02	TNX-601 Product Presentation
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: May 17, 2023

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

Exhibit 99.01

Tonix Pharmaceuticals Announces Pharmacology and Medicinal Chemistry Results that Reveal the Molecular Mechanism of Action of Tianeptine, the Active Ingredient of TNX-601 ER, in Treating Depression

Research Supports Direct Role for Restoring Neuroplasticity and Upsets Previously Held Beliefs About the Significance of Neurotransmitters in Treating Depression

Findings Explain Why Tianeptine Is Not Associated with Sexual Dysfunction and Weight Gain

Mechanism Supports Development of TNX-601 ER for a Broad Range of Neurodegenerative Diseases and Psychiatric Disorders

CHATHAM, N.J., May 17, 2023 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a clinical-stage biopharmaceutical company, today announced the molecular mechanism of action of tianeptine, the active ingredient of TNX-601 ER (tianeptine hemioxalate extended-release tablets), currently in Phase 2 clinical development for the treatment of major depressive disorder (MDD)*. Based on pharmacology and medicinal chemistry experiments, scientists at Tonix have established that tianeptine is an agonist for the nuclear peroxisome proliferator-activated receptor (PPAR) isoforms PPAR-β/δ and PPAR-γ, and tianeptine's effects on these PPAR isoforms account for its ability to induce neuroplasticity in cultured neurons.

The findings upset a long-held belief that the only way to restore the connectivity of neurons damaged in the state of depression was to increase the synaptic levels or activity of neurotransmitters such as the monoamines serotonin, norepinephrine, and dopamine. The new findings show that selective activation of nuclear PPAR-β/δ and PPAR-γ in neurons and supporting glia appears to be a more direct mechanism to achieve the goal of restoring neuronal connectivity, which is called neuroplasticity. Drugs that restore neuroplasticity are called plastogens.[1-3] Consequently, tianeptine is a plastogen that acts directly on nuclear receptors that regulate gene expression in neurons and microglia.

"The discovery that tianeptine stimulates neuroplasticity by activating certain PPAR isoforms could lead to a paradigm shift in designing new antidepressants, and change the relative reliance developers place on targeting synaptic neurotransmitter levels and activity," said Stephen Stahl, M.D., Ph.D., Adjunct Professor of Psychiatry at the University of California San Diego, Chairman of Neuroscience Education Institute, author of the bestselling clinical manual, *Essential Psychopharmacology Prescriber's Guide,* and consultant to Tonix. "This may lead to better pharmacological treatments for depression and for a range of neurodegenerative diseases in which neuronal connections are atrophying and the need to restore the connectivity is paramount to achieving more positive and more sustainable outcomes. Tianeptine avoids some of the more intolerable side effects of the traditional antidepressants because it cuts in line and intervenes downstream from the monoamine transporters and receptors."

The new research provides clarity on why tianeptine does not cause sexual dysfunction, weight gain, or several other treatment-limiting toxicities associated with traditional antidepressants. Tianeptine treats depression by activating select nuclear PPAR isoforms, and has little to do with monoaminergic neurotransmitters, which are known to be implicated in the most frequently cited side effects of most marketed antidepressants. Key experiments were performed by scientists at Tonix's Research and Development Center (RDC) in Frederick, Maryland.

"Understanding the mechanism of action of a molecule generally speeds its development and often points the way to broader clinical application," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "Despite its success in treating depression outside of the U.S. for more than 30 years, tianeptine's mechanism has remained obscure. Pioneering studies by Prof. Bruce McEwen, Ph.D. at Rockefeller University revealed that tianeptine stimulates stress-atrophied neurons to form new connections.[1] Subsequently, Prof. Ronald Duman, Ph.D. at Yale University discovered that enhancing these connections is a common principle underlying the therapeutic effects of traditional antidepressants, which only act indirectly on neuroplasticity by changing the level and activity of synaptic neurotransmitters."[4]

"In animal models, tianeptine restores neuroplasticity and reverses stress-induced impairments through activation of select nuclear PPAR isoforms without modulating synaptic monoamine neurotransmitters,"[1] said Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals. "Tianeptine mimics naturally occurring polyunsaturated fatty acid in binding to PPARs.[5] When compared to the traditional classes of antidepressants (SSRIs, tricyclics, etc.), the tianeptine sodium immediate release products available outside of the U.S. demonstrate comparable efficacy[6] and decreased side effects including sexual dysfunction[7-9], derangement of sleep architecture[10], sedating effects[11] despite anxiolysis, weight gain even with long term treatment[12], and cognitive impairment."[11, 13-15]

Dr. Sullivan continued, "Regarding potential future indications beyond our current program in MDD, the proposed mechanism is consistent with the clinical effects of tianeptine in promoting cognition in Alzheimer's disease, Parkinson's disease and bipolar disorder[14,15] and motivates us to develop

TNX-601 ER as a treatment for these and other conditions, in addition to our previously stated objectives to study it in posttraumatic stress disorder (PTSD) and corticosteroid-induced cognitive dysfunction. The PPAR-β/δ target is validated by prior work on agonists treating animal models of neurodegenerative and autoimmune disease of the central nervous system.[16] The PPAR-γ target is validated by prior work treating peripheral diabetes in animals and as FDA-approved drugs, and the concept that Alzheimer's can be considered a form of diabetes that affects the CNS, or type-III diabetes."[17]

Dr. Sullivan noted that the new Tonix findings about tianeptine's mechanism dispel the notion that tianeptine's weak μ-opioid receptor activity was central to its mechanism of treating depression.[18] This hypothesis was proposed based on results in the forced swim test (FST) using high-dose tianeptine in mice.[19] "Our work found no connection between tianeptine's neuroplastic effects on cultured neurons and its weak μ-opioid receptor agonism," Dr. Sullivan said. "In fact, we have identified a new chemical entity related to tianeptine, TNX-4300, that restores neuroplasticity in cultured neurons and is free from μ-opioid receptor activity."

Tonix is planning to submit data supporting tianeptine's mechanism of action for presentation at upcoming scientific conferences and for publication in peer reviewed journals.

* TNX-601 ER is an investigational new drug and is not approved for any indication

[1] McEwen, BS, et al. *Mol. Psychiatry* 2010, *15* (3), 237–249.

[2] Olson DE. *J Exp Neurosci*. 2018, 19;12:1179069518800508.

[3] Cooper T, et al. J*Psychopharmacol*. 2023, 37(3):242-247.

[4] Price RB, Duman R. *Mol Psychiatry* 2020, *25* (3), 530-543.

[5] Helmstädter M et al. *Int J Mol Sci.* 2022, 23(17):10070.

[6] Wagstaff AJ, et al. *CNS Drugs* 2001, *15* (3), 231-59.

[7] Bonierbale M, et al. *Curr Med Res Opin* 2003, *19* (2), 114-124

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[8] Ducrocq F. *Encephale* 1999, *25* (5), 515-6. French.

[9] Atmaca M, et al. *Hum Psychopharmacol* 2003, *18* (4), 277-80.

[10] Le Bon O. *Dialogues Clin Neurosci* 2005, *7* (4), 305-13.

[11] Yoon JS, et al. *Clin Psychopharmacol Neurosci* 2003, *1*, 27-34.

[12] Dalery J, et al. *Hum Psychopharmacol* 2001, *16* (S1), S39-S47.

[13] Jeon HJ, et al. *J Clin Psychopharmacol* 2014, *34* (2), 218-25.

[14] García-Alberca JM, et al. *J Alzheimer's Dis* 2022, *88* (2), 707-720.

[15] Kauer-Sant'Anna M, et al. *J Psychopharmacol* 2019, *33* (4), 502-510.

[16] Kahremany S et al. *Br J Pharmacol* 2015, 172(3):754-70

[17] Nguyen et al., *Int J Mol Sci.* 2010, 21(9):3165

[18] Samuels BA, et al. *Neuropsychopharmacol* 2017, *42* (10), 2052-2063.

[19] Reardon S. *Nature* 2019, *571* (7766), 456-457.

About Depression

According to the National Institute of Mental Health, an estimated 21 million adults in the U.S. in 2020 experienced at least one major depressive episode[1], with highest prevalence among individuals aged 18-25 at a rate of 17.0%. For approximately 2.5 million adults in the U.S., adjunctive therapies are necessary for depression treatment.[2,3] Depression is a condition characterized by symptoms such as a depressed mood or loss of interest or pleasure in daily activities most of the time for two weeks or more, accompanied by appetite changes, sleep disturbances, motor restlessness or retardation, loss of energy, feelings of worthlessness or excessive guilt, poor concentration, and suicidal thoughts and behaviors. These symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The majority of people who suffer from depression do not respond adequately to initial antidepressant therapy.[4]

[1] Data Courtesy of SAMHSA on Past Year Prevalence of Major Depressive Episode Among U.S. Adults 2020. Retrieved from http://www.nimh.nih.gov/health/statistics/major-depression.shtml

[2] IMS NSP, NPA, NDTI MAT-24-month data through Aug 2017.

[3] Kubitz N, et al. *PLoS One* 2013, *8* (10), e76882.

[4] Rush AJ, et al. *Am J. Psychiatry* 2007, *163* (11), 1905-1917.

About TNX-601 ER

TNX-601 ER (tianeptine hemioxalate extended-release tablets) is a novel oral formulation of tianeptine designed for once-daily daytime dosing in development as a candidate for the treatment for MDD, posttraumatic stress disorder, and neurocognitive dysfunction associated with corticosteroid

use. Tianeptine sodium (amorphous) immediate release (dosed 3 times daily) was first marketed for depression in France in 1989 and has been available for decades in Europe, Russia, Asia, and Latin America for the treatment of depression. Tianeptine sodium has an established safety profile from decades of use in these jurisdictions. Currently no tianeptine-containing is product approved in the U.S. and no extended-release tianeptine product is approved in any jurisdiction. Tonix discovered a novel oxalate salt of tianeptine that may provide improved stability, consistency, and manufacturability compared to known salt forms of tianeptine. In animal models, tianeptine restores dendritic arborization of pyramidal neurons in the CA3 region of hippocampus and in the dentate gyrus region promotes new neuron formation and integration into hippocampal networks.[1] Tianeptine's enhancement of neuroplasticity in animal models of stress is believed to be mediated by activation of PPAR isoforms PPAR-β/δ and PPAR-γ, which makes TNX-601 ER's properties distinct from traditional monoaminergic antidepressants in the U.S. and contributes to its potential for clinical indications beyond MDD and stress disorders. Tianeptine and its

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MC5 metabolite are also weak mu-opioid receptor (MOR) agonists that present a potential abuse liability if illicitly misused in large quantities (typically abused at 8-80 times the therapeutic dose on a daily basis[2]). In patients who were prescribed tianeptine for depression, the French Transparency Committee found an incidence of misuse of approximately 1 case per 1,000 patients treated[3] suggesting low abuse liability when used at the antidepressant dose in patients prescribed tianeptine for depression. Clinical trials have shown that cessation of a therapeutic course of tianeptine does not appear to result in dependence or withdrawal symptoms following 6-weeks[4-8], 3-months[9], or 12-months[10] of treatment. The ER formulation of TNX-601 includes several potentially abuse deterrent ingredients include gel forming polymers which impede extraction. In addition, the tablet's hardness makes it difficult to crush, cut or grind to fine particle size, which potentially hinders efforts to misuse by insufflation or intravenous routes. Tianeptine's reported pro-cognitive and anxiolytic effects as well as its ability to attenuate the neuropathological effects of excessive stress responses suggest that it may also be used to treat posttraumatic stress disorder (PTSD), and neurocognitive dysfunction associated with corticosteroid use. TNX-601 ER is expected to have patent protection through 2037.

[1] McEwen, B. S., et al. *Mol. Psychiatry* 2010, *15* (3), 237–249.

[2] Lauhan, R., et al. *Psychosomatics* 2018, *59* (6), 547–53.

[3] Haute Authorite de Sante; Transparency Committee Opinion. Stablon 12.5 Mg, Coated Tablet, Re- Assessment of Actual Benefit at the Request of the Transparency Committee. December 5, 2012.

[4] Emsley, R., et al. *J. Clin. Psychiatry* 2018, *79* (4)

[5] Bonierbale M, et al. *Curr Med Res Opin* 2003, *19*(2):114-124.

[6] Guelfi, J. D., et al. *Neuropsychobiology* 1989, *22* (1), 41–48.

[7] Invernizzi, G. et al., *Neuropsychobiology* 1994, *30* (2–3), 85–93.

[8] Lepine, J. P., et al. *Hum. Psychopharmacol.* 2001, *16* (3), 219–227.

[9] Guelfi, J. D. et al., *Neuropsychobiology* 1992, *25* (3), 140–148.

[10] Lôo, H. et al., *Br. J. Psychiatry. Suppl.* 1992, *15*, 61–65.

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 topline data expected in the fourth quarter of 2023. TNX-102 SL is also being developed to treat Long COVID, a chronic post-acute COVID-19 condition. Enrollment in a Phase 2 study has been completed, and topline results are expected in the third quarter of 2023. TNX-1900 (intranasal potentiated oxytocin), in development for chronic migraine, is currently enrolling with topline data expected in the fourth quarter of 2023. TNX-601 ER (tianeptine hemioxalate extended-release tablets), a once-daily formulation 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 third 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

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antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. A Phase 1 study of TNX-1500 is expected to be initiated in the third 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 and TNX-4000, classes 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.*

This press release and further information about Tonix can be found at www.tonixpharma.com.

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.

TONIX PHARMACEUTICALS

Major Depressive Disorder (MDD)

Epidemiology and Characteristics of Depression

- Major depressive disorder (MDD) is a leading cause of disability worldwide, with 21 million adults in the US alone experiencing a depressive episode in 2020[1]
- Lifetime prevalence of 16%, and associated with important psychological suffering, as well as elevated rates of suicide and worse prognosis of comorbid medical conditions[2,3]
- Highly comorbid with other psychiatric disorders (e.g., anxiety disorders, substance use disorders) as well as medical conditions (e.g., cardiovascular disease, metabolic syndromes, respiratory diseases, various deficiencies, infections, collagen disorders, endocrine diseases, etc.)
- Hormonal aspects can significantly impact course and treatment (especially evident in post-partum depression)
- Most treatment guidelines support use of antidepressants in moderate to severe MDD

[1]Substance Abuse and Mental Health Services Administration (SAMHSA). 2020. Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health.
[2]Kupfer et al., 2012. *The Lancet.* 379, 1045–1055
[3]Otte et al., 2016. *Nat. Rev. Dis. Primer.* 2:16065

High Unmet Need for New Classes of Antidepressants

- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, regarded as the largest antidepressant trial ever conducted, indicated **approximately 30% of depressed patients fail to achieve remission**, even after multiple treatment attempts[1,2]
- SSRIs are currently the most prescribed class of antidepressants, **yet only about 50% of patients with MDD respond to initial SSRI treatment**, and only 35-40% of those patients achieve full remission[1]
- Antidepressant treatments often continue for years, and the **side effect profiles of the monoaminergic antidepressants are intolerable to many**
- There is a high unmet need for new classes of antidepressants with **different mechanisms of action**

[1]Rush et al., 2006. *Am J Psychiatry.* 163:1905–1917
[2]Rush et al., 2004. *Control Clin Trials.* 25(1):119-42

TNX-601 ER*: Depression
Tianeptine Hemioxalate Extended-Release Tablets (39.4 mg)

PROFILE

- A novel, oral, extended-release once-daily tablet
- Treatment effect of tianeptine sodium immediate release *t.i.d.* in depression is well-established
- Tianeptine restores neuroplasticity in animal models
- Indirectly modulates the glutamatergic system
- Does not interact with AMPA, NMDA or kainate receptors[1]

Differentiators:

Relative to tianeptine IR available ex-US:

- Once daily dosing

Relative to traditional antidepressants:

- Unique mechanism of action – beyond neurotransmitter modulation
- Tianeptine sodium IR has similar efficacy but fewer side effects than traditional antidepressants

Patents Issued

DEVELOPMENT PROGRAM

Market Entry: Major Depressive Disorder (MDD)

Additional Indications: PTSD, Neurocognitive Disorder From Corticosteroids, Alzheimer's Disease[2]

Status: Phase 2 MDD study UPLIFT is currently enrolling

Next Steps: Interim analysis results on first 50% of sample expected 4Q 2023

*TNX-601 ER has not been approved for any indication.

[1]AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA=N-methyl-D-aspartate
[2]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720

TNX-601 ER - Phase 2 UPLIFT* Study Design

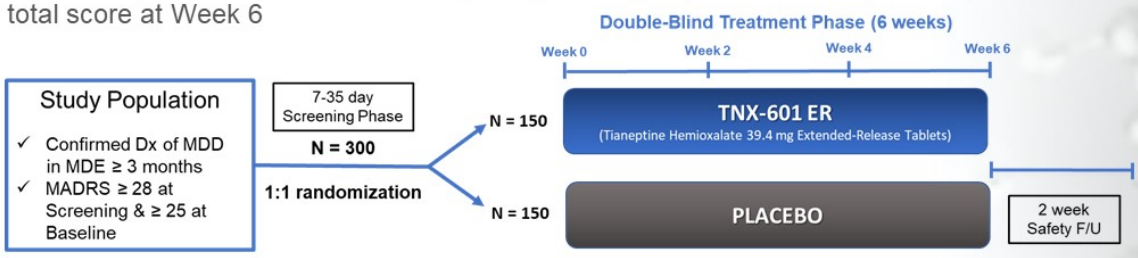
UPLIFT Study

General study characteristics:

- Randomized, double-blind, placebo-controlled study in Major Depressive Disorder to evaluate monotherapy with TNX-601 ER versus placebo
- Parallel design with two arms – treatment with tianeptine hemioxalate 39.4 mg or placebo
- ~30 U.S. sites only, expected to enroll approximately 300 patients
- One unblinded interim analysis based on 50% of randomized participants expected 4Q'23

Primary Endpoint:

- Mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6



*ClinicalTrials.gov Identifier: NCT05686408

Abbreviations: Dx, diagnosis; ER, extended-release; F/U, follow-up; MDD, major depressive disorder; MDE, major depressive episode; N, number

History of Tianeptine and TNX-601 ER

- Tianeptine sodium (amorphous) immediate release (IR) tablets have been available in Europe and many countries in Asia and Latin America for the treatment of MDD since it was first marketed in France in 1989. Due to its short half-life, tianeptine sodium IR is taken three times daily, which is challenging for patient adherence.
- Currently, there is no tianeptine-containing product approved in the U.S. and no extended-release tianeptine product approved anywhere in the world.
- Tonix discovered a novel hemioxalate salt of tianeptine that may provide **improved stability, consistency, and manufacturability** compared to known salt forms of tianeptine.
- TNX-601 ER is **taken once daily, increasing patient adherence** and is thereby anticipated to improve the overall effectiveness of treatment compared to that of tianeptine sodium IR.

Proposed MOA of Tianeptine

Distinct compared to other antidepressants currently marketed in the U.S.

- In Table[1] (right), it is illustrated how downstream effects of AD actions on neuroplasticity, including enhanced neurogenesis, contribute to improvements in *both mood and cognitive function*
- Tianeptine additionally has neuroprotective effects against hypoxia and deleterious effects of inflammatory cytokines in cortex and white matter[2]
- Tianeptine additionally has partially protective effects on the changes in microglia viability/death evoked by lipopolysaccharide[3]
- And >30 years of real-world experience with tianeptine for depression ex-US support its unique aspects, heretofore unavailable in US

	Untreated Depression	Treated Depression
Behavior	↓Memory ↑Rumination ↑Negative Affect	↑Memory ↓Negative Affect
Network	↑Hippocampal-Amygdala connectivity during negative emotional recall ↓Hippocampal-Amygdala connectivity at rest	↓Hippocampal-Prefrontal cortex connectivity at rest
Neurons	↓Neurogenesis ↓Pyramidal Cells ↓Granule Neurons ↓Dendrites	↑Neurogenesis ↑Dendrites ↑Granule Neurons
Synapses	↓AMPA Receptors ↓Spine Density ↓LTP ↑LTD ↓Spine Complexity	↑LTP ↑Spine Density ↓LTD ↑Spine Complexity
Molecules (BDNF, mTOR)	↓BDNF ↑Glutamate ↓mTOR	↑BDNF ↑Glutamate

[1]Tartt et al., 2022. *Molecular Psychiatry* 27: 2689–2699.
[2]Plaisant et al.,2003. *Neuropharmacology* 44: 801–809.
[3]Slusarczyk et al., 2018. *Int J Mol Sci* 19: 1965.

Clinical Trials of Tianeptine Sodium

Placebo-controlled and comparative trials in depression

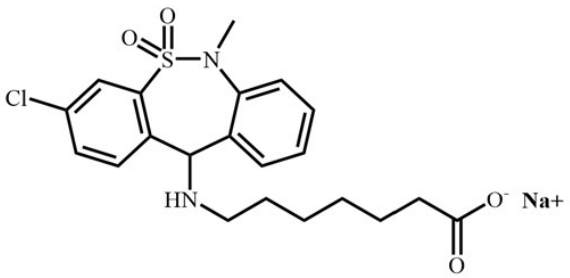
- Antidepressant efficacy confirmed in multicenter double-blind, placebo-controlled, randomized trials[1,2]
- Enriched enrollment randomized withdrawal design trial of long-term (16.5 months) treatment demonstrated reduction of MDD relapse and recurrence by 2- to 3-fold compared to placebo[3]
- Head-to-head comparisons showing equivalent efficacy of tianeptine with:
  - TCAs
    - Imipramine[1]
    - Amitriptyline[4,5,6]
  - SSRIs
    - Fluoxetine[4,7]
    - Sertraline[8]
    - Paroxetine[9,10,11]
    - Escitalopram[12]
  - Mianserin[13]
- Rigorous meta-analysis[14,15] of studies comparing tianeptine to SSRIs concluded tianeptine at least as effective as SSRIs, and trend noted for better overall acceptability profile in treatment of depressed patients

[1]Cassono et al., 1996. *Eur Psychiatry*.11(5):254-9
[2]Costa e Silva et al., 1997. *Neuropsychobiology*. 35(1):24-9
[3]Dalery et al., 2001. *Hum Psychopharmacol*.16(S1):S39-S47
[4]Lôo et al., 1999. *Neuropsychobiology*.19(2):79-85
[5]Guelfi et al., 1989. *Neuropsychobiology*. 22(1):41-8
[6]Invernizzi et al., 1994. *Neuropsychobiology*. 30(2-3):85-93
[7]Novotny et al., 2002. *Hum Psychopharmacol*. 17(6):299-303
[8]Szádóczky et al., 2002. *Encephale*. 28(4):343-9
[9]Lepine et al., 2001. *Hum Psychopharmacol*. 16(3):219-227
[10]Waintraub et al., 2002. *CNS Drugs*. 16(1):65-75
[11]Nickel et al., 2003. *J Clin Psychopharmacol*. 23(2):155-68
[12]Emsley et al., 2018. J Clin Psychiatry. 79(4):17m11741
[13]Brion et al., 1996. *Presse Med*. 25(9):461-8
[14]Kasper et al., 2002. *Eur Psychiatry*. 17 Suppl 3:331-40
[15]Olié et al., 2003. *Encephale*. 29(4 Pt 1):322-8

Tianeptine Sodium

First marketed in France over thirty years ago

- Tianeptine discovered and patented by French Society of Medical Research in 1960s
- Tianeptine first marketed in 1989 for the treatment of major depression by French pharmaceutical company Servier Laboratories under the trade name Stablon®
- Currently marketed in over 60 countries in Europe, Asia, and South America

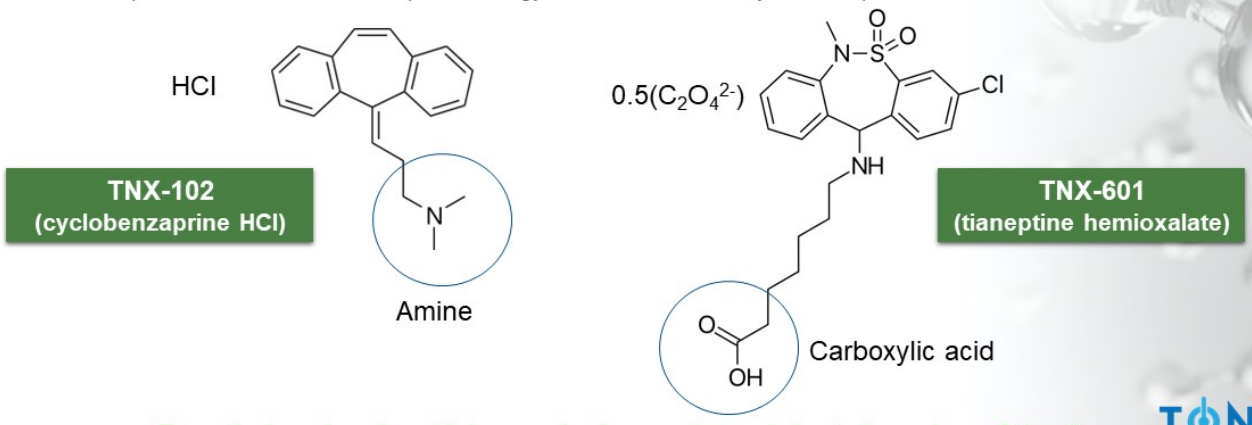


[3-chloro-6-methyl-5,5-dioxo-6,11-dihydro-(c,f)-dibenzo-(1,2-thiazepine)-11-yl) amino]-7 heptanoic acid, sodium salt

Structural Comparison: Tricyclic and TNX-601

Cyclobenzaprine and tianeptine share structural similarities with classic tricyclic antidepressants (TCAs) and to each other, but each has unique pharmacological profile

- Tricyclic nucleus, but 7-carbon straight chain fatty acid side chain terminates with a carboxylic acid
  - Tianeptine's side chain terminates in a carboxylic acid
  - Tianeptine's side chain results in a pharmacology that is distinct from tricyclic antidepressants



Tianeptine's carboxylic acid changes its pharmacology relative to the amines of tricyclics

Tianeptine is a Polyunsaturated Fatty Acid (PUFA) Analogue

PUFAs and PUFA-analogues

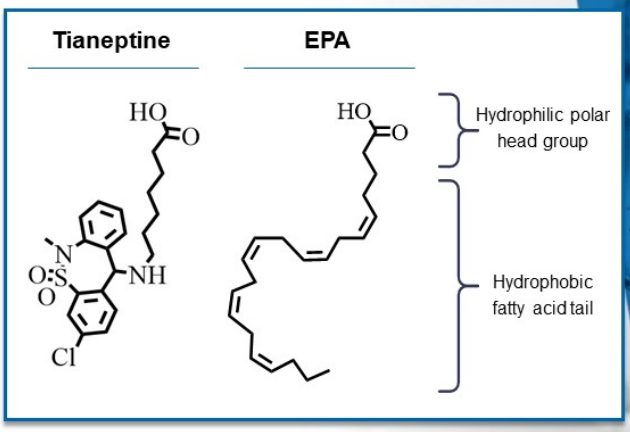
- Polar acidic "head" and hydrophobic fatty acid "tail"

Pharmacological modulation of PUFA signaling has therapeutic potential in multiple pathologies

- Act through the binding sites of endogenous FA metabolites on enzymes, transporters, and receptors
- Several PUFA analogues have been developed as drugs, including the ethyl ester of eicosapentaenoic Acid (EPA)[1] which is branded as Vascepa®

PUFAs and PUFA-analogues have distinctive ligand-target interactions with PUFA binding proteins

- PUFA binding sites share common chemical features: low affinity[2,3] and low off-rate
- Traditional PUFA selectivity has been limited



EC_{50} for EPA is ~3 µM

[1]EPA = eicosa-5Z, 8Z, 11Z, 14Z, 17Z-pentaenoic acid.
[2]Xu et al., 1999. *Mol Cell.* 3(3):397-403.
[3]Helmstädter et al., 2022. *Int J Mol Sci.* 23(17):10070.

EPA and DHA are Examples of Polyunsaturated Fatty Acids (PUFAs)

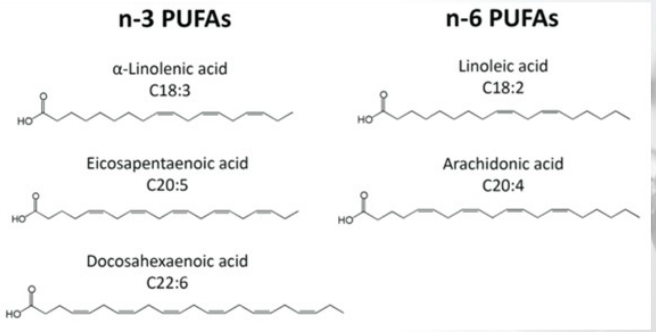
Eicosapentaenoic acid (EPA)[2]

- Essential PUFA – obtained from diet
- EPA is the active ingredient in Vascepa® (ethyl-ester EPA prodrug) which reduces heart attacks, stroke and death in statin-resistant hyper-triglyceridemia

Docosahexaenoic acid (DHA)[3]

- Primary structural component of the brain
- Most abundant omega-3 fatty acid in the brain and retina
- Comprises 40% of the PUFAs in the brain and 60% of the PUFAs in the retina

PUFAs[1]



EPA and DHA have activity in treating MDD[4,5]

- Activity shown in studies and meta-analyses, but insufficient randomized studies to be conclusive

[1]Bohannon et al., 2023. *bioRxiv* preprint
[2]Wikipedia: https://en.wikipedia.org/wiki/Eicosapentaenoic_acid
[3]Wikipedia: https://en.wikipedia.org/wiki/Docosahexaenoic_acid
[4]Liao et al., 2019. *Transl Psychiatry*. 9(1):190
[5]Wani et al., 2015. *Integr Med Res*. 4(3):132-141

TONIX PHARMACEUTICALS

Observations that Relate Tianeptine's Action to PPAR Activation

Tianeptine is an agonist at PPAR-β/δ and PPAR-γ

- Tianeptine selectively activates PPAR-β/δ and PPAR-γ, but not PPAR-α[1]
  - Regulates PPAR-β/δ and PPAR-γ driven transcription
  - Tianeptine metabolite MC5 does not activate PPAR-β/δ or PPAR-γ
- Tianeptine's neuroplastic effects on cultured neurons correlate with PPAR-β/δ and PPAR-γ agonism[1]
  - TNX-4300 is a new chemical entity, that activates PPAR-β/δ and PPAR-γ and restores neuroplasticity in cultured neurons
- Company plans to submit data supporting tianeptine's mechanism of action to upcoming scientific conferences and for publication

[1]Data on file - Tonix

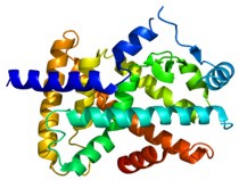
TONIX PHARMACEUTICALS

Peroxisome Proliferator Activated-Receptor (PPAR) Family: PPAR-β/δ

PPAR-α[1]

Expression
Liver, muscle, heart

Known roles
FA oxidation

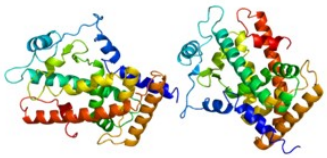


Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png

PPAR-β/δ[1,2]

Expression
Brain, skeletal muscle, adipose tissue, microglia, lungs, skin

Known roles
Promotes CNS neurotrophic factors and reduces expression of inflammatory mediators

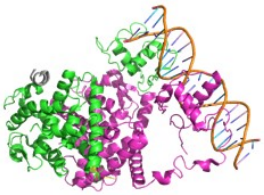


Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png

PPAR-γ[1]

Expression
Endothelial and smooth muscle cells

Known roles
Adipocyte differentiation regulation, FA storage, glucose metabolism



A2-33. Wikimedia Commons. March 14, 2012. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:PPARG.png

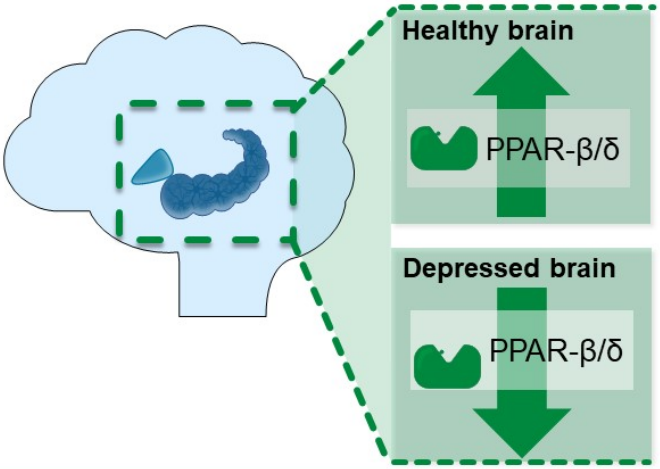
[1]Tyagi et al., 2011. *J Adv Pharm Technol Res.* 2(4):236-240
[2]D'Angelo et al., 2011. *J Cell Physiol.* 226(8):2170-2180

PPAR-β/δ Protects Against Pathology in CNS Animal Models

- PPAR-β/δ normally protects against pathophysiological processes in the nervous system[1]
  - PPAR-β/δ also plays roles in neuronal development and function
- PPAR-β/δ-deficient mice exhibited abnormal neurophysiological processes
  - Decreased myelination, augmented inflammatory reactions and low score in memory tests[2]
  - Tau (τ) hyperphosphorylation, astrogliosis and CNS inflammation[3]
  - Worse outcome after cerebral ischemia with defective antioxidant responses[4,5]
- Selective PPAR-β/δ agonists improve outcome after:
  - Experimental Autoimmune Encephalomyelitis[6]
  - Experimental cerebral ischemia[7]
  - Transgenic model of Alzheimer's[8]
  - Spinal cord trauma[9]
  - Ischemic stroke related vascular dysfunction[10]
  - Chemically induced Parkinson's[7,11]

[1]Kahremany et al., 2015. *Br J Pharmacol.* 172(3):754-70
[2]Peters et al., 2000. *Mol Cell Biol.* 20:5119–5128
[3]Barroso et al., 2013. *Biochim Biophys Acta.* 1832:1241–1248
[4]Arsenijevic D, et al. *J Cereb Blood Flow Metab.* 2006;26:433–445
[5]Pialat et al., 2007. *NMR Biomed.* 20:335–342
[6]Polak et al., 2005. *J Neuroimmunol.* 168:65–75
[7]Iwashita et al., 2007. *J Pharmacol Exp Ther.* 320:1087–1096
[8]Kalinin et al., 2009. *Curr Alzheimer Res.* 6:431–437
[9]Paterniti et al., 2010. *J Pharmacol Exp Ther.* 333:465–477
[10]Yin et al., 2010. *J Neurosci.* 30:6398–6408
[11]Martin et al., 2013. *Neuroscience.* 240:191–203

Peroxisome Proliferator-Activated Receptor Delta (PPAR-β/δ)



- In the brain, PPAR-β/δ is found at high levels in the hypothalamus and hippocampus[1,2]
- Chronic stress reduces PPAR-β/δ, whereas overexpression or activation of hippocampal PPAR-β/δ produces antidepressant-like effects[3,4]

PPAR-β/δ upregulation/activation is associated with the upregulation of neurotrophic growth factors, such as BDNF[1]

BDNF=brain-derived neurotrophic factor

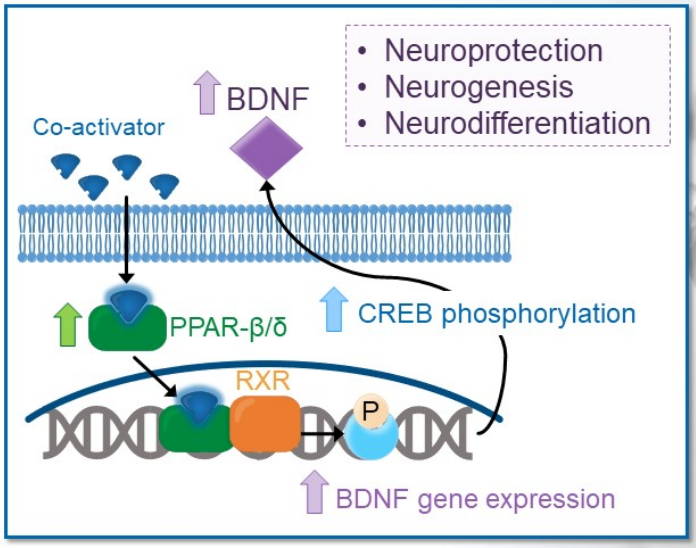
[1]Woods et al., 2003. *Brain Res.* 975(1-2):10-21
[2]Higashiyama et al., 2007. *Histochem Cell Biol.* 127(5):485-494
[3]Chen et al., 2019. *Int J Neuropsychopharmacol.* 22(6):372-382
[4]Liu et al., 2017. *Clin Exp Pharmacol Physiol.* 44(6):664-670

TONIX PHARMACEUTICALS

Peroxisome Proliferator-Activated Receptor Delta (PPAR-β/δ)

PPAR-β/δ upregulation or agonists improve depressive symptoms by upregulating neurotrophic growth factors like BDNF[1]

- mBDNF downregulation is correlated with decreased levels of CREB phosphorylation and mBDNF[1,2]
- PPAR-β/δ upregulation increased these levels[1]



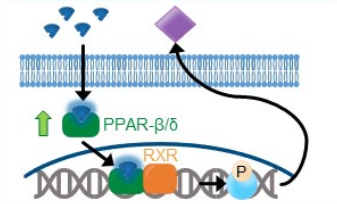
BDNF = brain-derived neurotrophic factor
CREB = cAMP response element binding protein
mBDNF = mature BDNF

[1]Ji et al., 2015. *Int J Neuropsychopharmacol.* 19(1):pyv083
[2]Liu et al., 2017. *Clin Exp Pharmacol Physiol.* 44(6):664-670

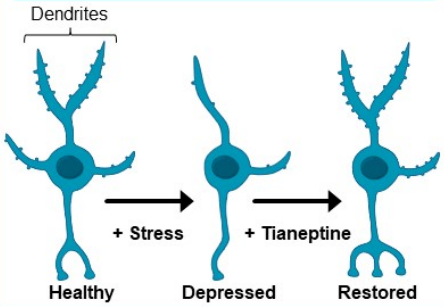
TONIX PHARMACEUTICALS

Tianeptine Helps Restore Stress-Related Hippocampal Remodeling

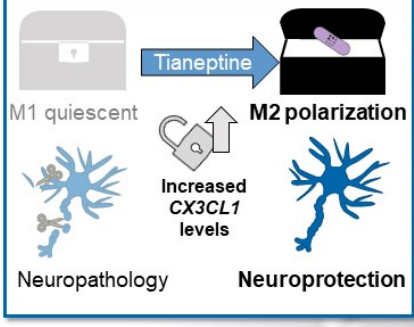
Tianeptine activation of PPAR-β/δ appears related to tianeptine's known effect on reducing inflammation and encouraging neuronal growth and development[1,2]



Tianeptine administration reversed stress-induced dendrite shrinkage in hippocampal CA3 dendrites[3]



Tianeptine normalizes *CX3CL1* levels and polarizes microglia to M2 activation[4]

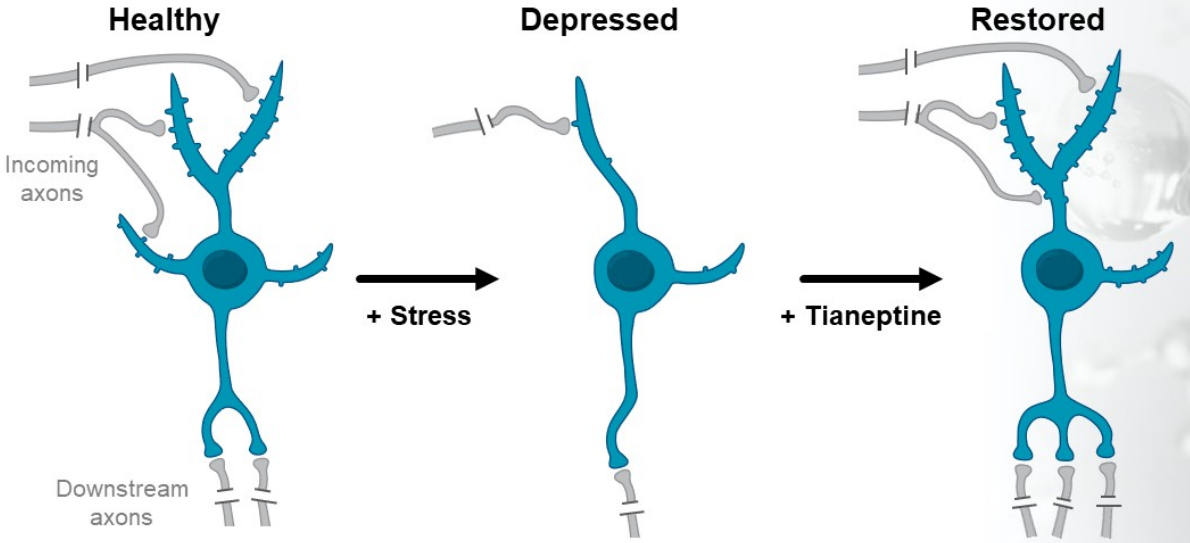


Tianeptine activation of PPAR-β/δ regulates the expression of genes that stimulate dendrite arborization and reduce proinflammatory microglia activation. By these activities, tianeptine is thought to treat depression at the neuroplastic and neurogenerative levels[1-4]

[1]Ji et al., 2015. *Int J Neuropsychopharmacol*. 19(1):pyv083
[2]Liu et al., 2017. *Clin Exp Pharmacol Physiol*. 44(6):664-670
[3]Magariños et al., 1999. *Eur J Pharmacol*. 371(2-3):113-122
[4]Trojan et al., 2017. *Front Pharmacol*. 8:779

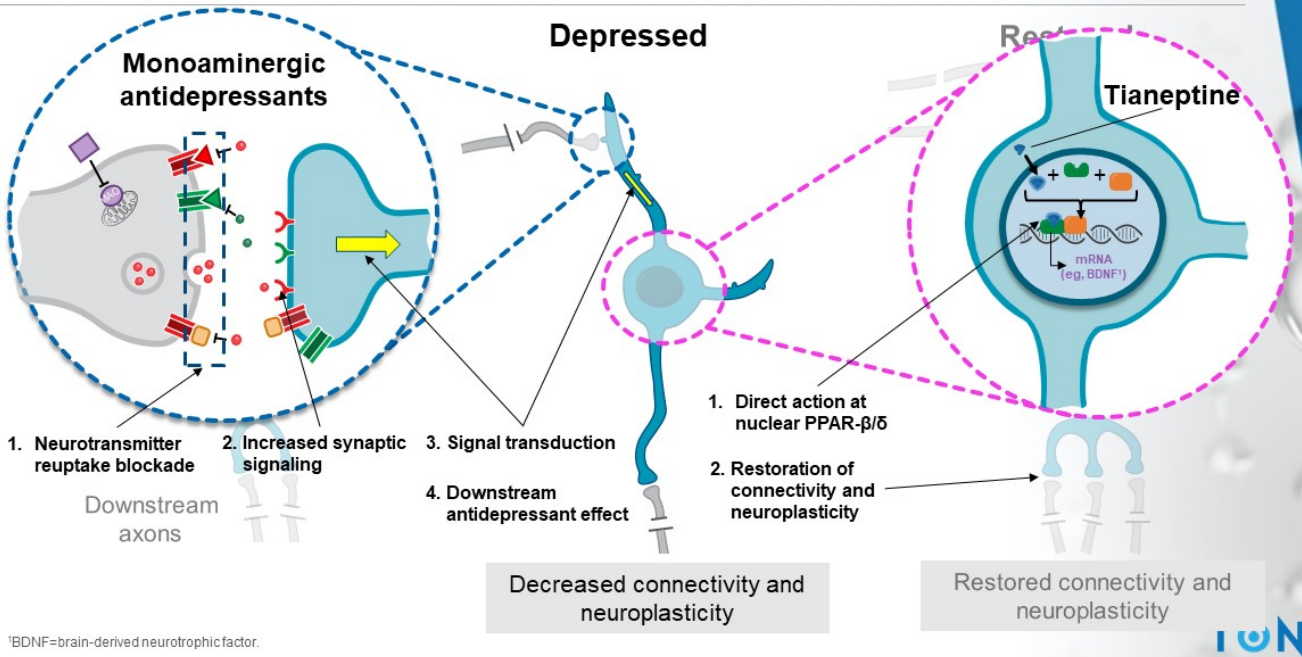
TONIX PHARMACEUTICALS

Tianeptine Restores Neuronal Connectivity and Neuroplasticity in Animal Models



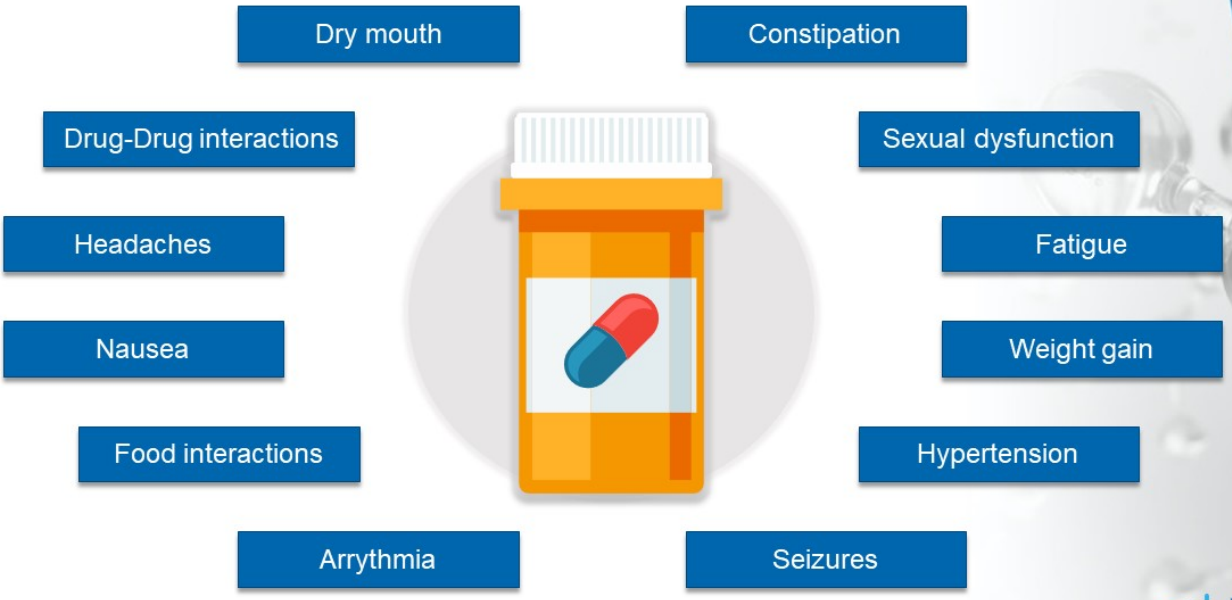
TONIX PHARMACEUTICALS

While Monoaminergic Antidepressants Work at the Synapse, Tianeptine "Cuts in Line" to More Directly Affect Neuroplasticity



[1]BDNF=brain-derived neurotrophic factor.

Potential Side Effects of Monoaminergic Antidepressants Related to Neurotransmitter Modulation

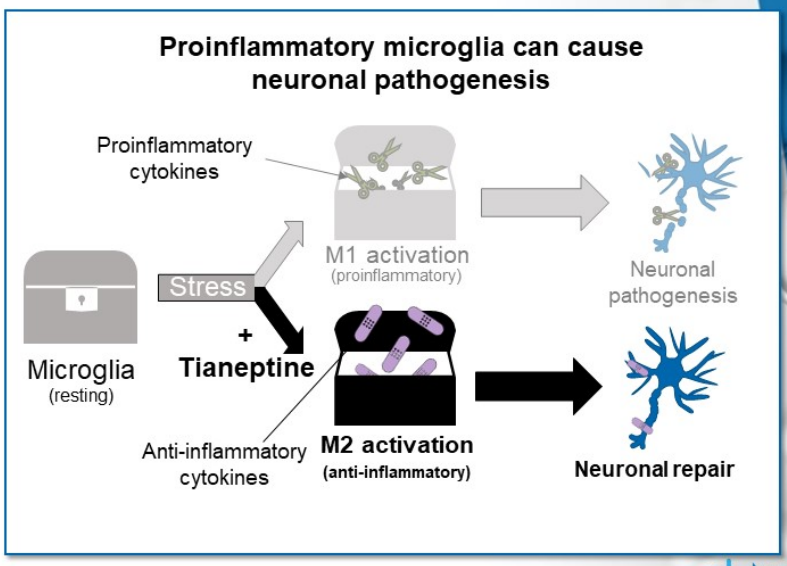


Gelenberg et al., 2010. *Am J Psychiatry*.167(suppl):1-152

Tianeptine Acts on Microglia in the Hippocampus to Facilitate Neuronal Remodeling Under Stress

Microglia and neurogenesis

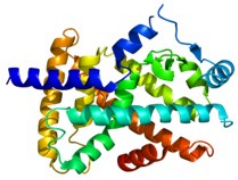
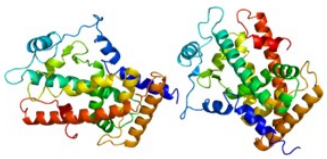
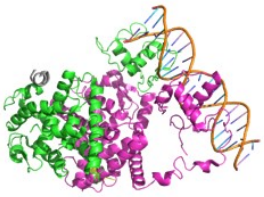
- Microglia are immune effector cells[1]
- Under normal conditions, microglia regulate synaptic transmission, prune neuronal synapses, and assist in the formation of neural circuits[1,2]
- When homeostasis is disrupted, microglia may activate and release proinflammatory cytokines and inhibit normal neuronal growth[1,2]
- Tianeptine acts on microglia to bias response towards M2 activation by normalizing *CX3CL1* levels[3]



[1]Wang et al., 2022. *J Neuroinflammation*. 19(1):132
[2]Pawelec et al., 2020. *Cells*. 9(10):2277
[3]Trojan et al., 2017. *Front Pharmacol*. 8:779

TONIX PHARMACEUTICALS

PPAR Family Members: PPAR-γ

PPAR-α[1]	PPAR-β/δ[1,2]	PPAR-γ[1]
Expression Liver, muscle, heart	**Expression** Brain, skeletal muscle, adipose tissue, microglia, lungs, skin	**Expression** Endothelial and smooth muscle cells
Known roles FA oxidation	**Known roles** Promotes CNS neurotrophic factors and reduces expression of inflammatory mediators	**Known roles** Adipocyte differentiation regulation, FA storage, glucose metabolism
		
Emw. Wikimedia Commons. February 10, 2010. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARA_PDB_1i7g.png	Emw. Wikimedia Commons. December 15, 2009. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:Protein_PPARD_PDB_1gwx.png	A2-33. Wikimedia Commons. March 14, 2012. Accessed March 31, 2022. https://commons.wikimedia.org/wiki/File:PPARG.png

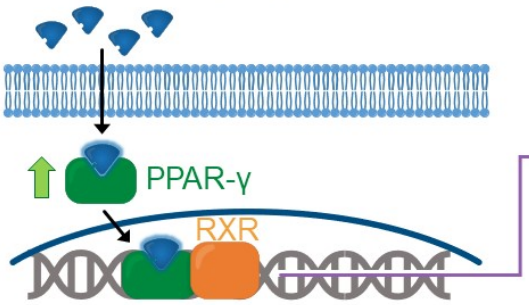
[1]Tyagi et al., 2011. *J Adv Pharm Technol Res*. 2(4):236-240
[2]D'Angelo et al., 2011. *J Cell Physiol*. 226(8):2170-2180

TONIX PHARMACEUTICALS

PPAR-γ Restores Glucose-Sensing Ability in Type 2 Diabetes

Diabetes defines a group of diseases whose common trait is high blood sugar levels, which can result in damage to neurons, kidneys, eyes, and blood vessels

Thiazolidinediones (TZDs)



Glucose metabolism

- Insulin receptor substrate 1 (IRS-1)
- Insulin receptor substrate 2 (IRS-2)
- P85 subunit of PI3K
- CAP

Restore glucose-sensing ability

In type 2 diabetes, the agonist class of TZDs has been shown to restore glucose-sensing ability (decrease insulin resistance) and trigger activation of insulin-responsive genes

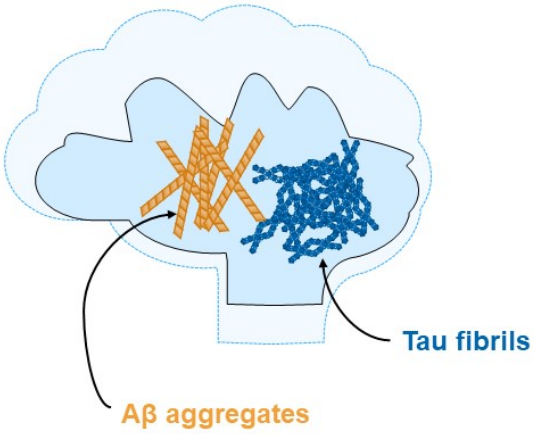
CAP=catabolite activator protein
PI3K=phosphatidylinositol 3-kinase

Kim et al., 2004. *Diabetologia.* 47(12):2215-2225

TONIX PHARMACEUTICALS

Diabetes Is a Risk Factor for Neurodegenerative Diseases Like Alzheimer's Disease (AD)

AD is a neurodegenerative disease characterized by brain cell death largely attributed to amyloid plaques and neurofibrillary tangles

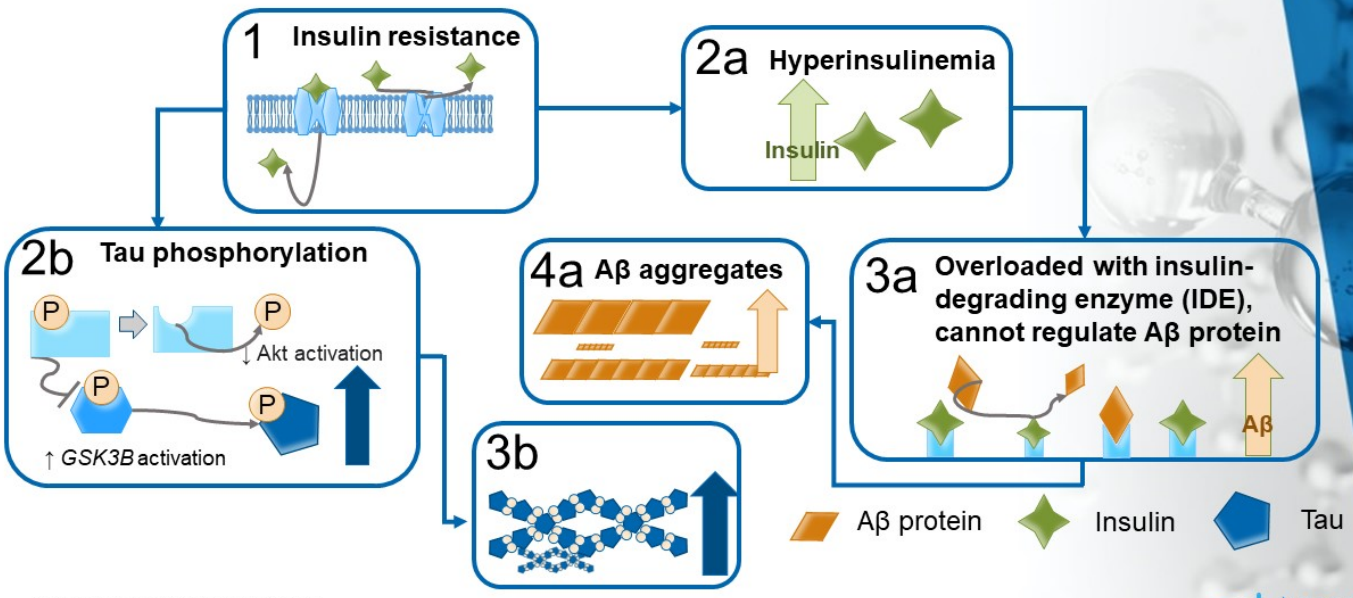


While type 2 diabetes has long been considered a risk factor for AD, type 3 diabetes is a newly recognized category of diabetes centered around **insulin resistance within the brain**

[1]Nguyen et al., 2010. *Int J Mol Sci.* 21(9):3165
[2]Kandimalla et al., 2017. *Biochim Biophys Acta Mol Basis Dis.* 1863(5):1078-1089
[3]Pugazhenthi et al., 2017. *Biochim Biophys Acta Mol Basis Dis.* 1863(5):1037-1045

TONIX PHARMACEUTICALS

The Relationship Between Type 3 Diabetes and Alzheimer's



[1]Nguyen et al., 2010. *Int J Mol Sci*. 21(9):3165
[2]Kandimalla et al., 2017. *Biochim Biophys Acta Mol Basis Dis*. 1863(5):1078-1089
[3]Pugazhenthi et al., 2017. *Biochim Biophys Acta Mol Basis Dis*. 1863(5):1037-1045

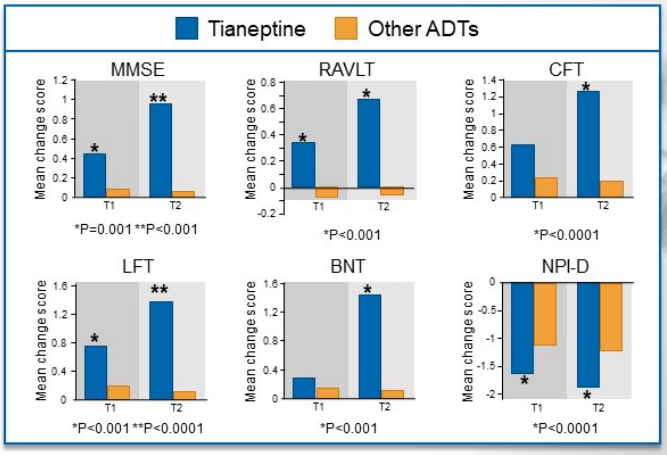
TONIX PHARMACEUTICALS

Tianeptine Has Pro-cognitive Effects in Alzheimer's and Bipolar

After 12 months, patients with AD on tianeptine demonstrated improvements on most cognitive measurements[1]

Significant results from the linear mixed models for cognition and depression performances

- MMSE: Mini-Mental State Examination
- RAVLT: Rey Auditory Verbal Learning Test
- CFT: Category Fluency Test
- LFT: Letter Fluency Test
- BNT: Boston Naming Test
- NPI-D: Neuropsychiatric Inventory Depression subscale
- T0=baseline, T1=follow-up 6 months, T2=follow-up 12 months



An additional study showed that after 24 weeks on tianeptine, patients with bipolar disorder performed better on the Wechsler Adult Intelligence Scale subtest, with improvements on most cognitive measurements[2]

[1]García-Alberca et al., 2022. *J Alzheimers Dis*. 88(2):707-720
[2]Kauer-Sant'Anna et al., 2019. *J Psychopharmacol*. 33(4):502-510

TONIX PHARMACEUTICALS

Tianeptine's off-target activity

Illicit or unregulated introduction of the drug substance to the United States

- Because of low affinity binding and agonist activity on μ-opioid receptor[1], there is the potential abuse liability of tianeptine drug substance when available in large quantities by
  - People seeking a μ-opioid "high"
  - People self-managing withdrawal effects from opioids

- Based on these μ–opioid data and interpretations,[1] unregulated tianeptine entered the US
  - As a research chemical - *not for human use*
  - As an ingredient in food supplements sold over the counter
  - Without any submitted data or regulatory status, promoted as a "smart drug" (nootropic) sold over the internet

[1]Gassaway et al., 2014. *Transl Psychiatry*. 4(7):e411

Observations that Relate Tianeptine's Action to μ-Opioid Receptors

Tianeptine is a weak μ-opiate receptor agonist

- In 2014, tianeptine was reported to be a weak μ–opioid agonist[1]
  - K_i = 383 nM and EC_{50} = 194 nM[1]
  - Others have found even lower binding and activity, e.g., K_i = 768 nM[2] or EC_{50} >3 uM[3]

- In 2017, tianeptine's μ–opioid activity was implicated as central to its mechanism of treating depression[4,5]
  - The effect of tianeptine at 30 mg/kg on the Porsolt Forced Swim Test (FST) was decreased by naloxone treatment or in knock-out mice lacking the μ–opioid receptor
  - Some μ–opioid receptor agonists have a signal in the FST[6-8], which complicates the interpretation of tianeptine effects

- In 2023, using medicinal chemistry and pharmacology, scientists at Tonix found no connection between tianeptine's neuroplastic effects on cultured neurons and its weak μ–opioid receptor agonism[9]
  - Identified a new chemical entity, TNX-4300 that restores neuroplasticity in cultured neurons and is free from μ–opioid receptor activity[9]

[1]Gassaway et al., 2014. *Transl Psychiatry*. 4(7):e411
[2]BL Roth PDSP K$_i$ database; https://pdsp.unc.edu/databases
[3]Vandeputte et al., 2020. *Arch Toxicol*. 94(11):3819-3830
[4]Samuels et al., 2017. *Neuropsychopharmacology*. 42(10):2052-2063
[5]Han et al., 2022. *Neuropsychopharmacology*. 47(7):1387-1397
[6]Szumiec L, et al. *Behav Brain Res*. 2023. 3:114466.
[7]Zomkowski AD, et al., *Neurosci Lett*. 2005. 381(3):279-83.
[8]Falcon E, et al. *Psychopharmacology (Berl)*. 2015 232(5):907-15.
[9]Data on file - Tonix

Prescription Tianeptine has Low Incidence of Abuse

Low activity at μ-opioid receptor is associated with low misuse of prescription oral tianeptine

- Tianeptine and its MC5 metabolite are weak opioid (μ-opioid) receptor (MOR) agonists[1] that present a potential abuse liability if illicitly misused in large quantities
  - Typically abused at 8-80 times the therapeutic dose on a daily basis[2].
- Post-marketing research in France showed that in patients who were prescribed tianeptine for depression, the incidence of misuse was approximately 1 case per 1,000 patients treated[3]
  - Suggests low abuse liability when used at the antidepressant dose
- Clinical trials have shown that abrupt cessation of a therapeutic course of tianeptine does not result in dependence or withdrawal symptoms following a treatment duration of:
  - 6-weeks[4-8]
  - 3-months[9]
  - 12-months[10]

[1]Gassaway et al., 2014. *Transl Psychiatry.* 4(7):e411
[2]Lauhan et al., 2018. *Psychosomatics.* 59(6), 547–53
[3]Haute Authorite de Sante. Transparency Committee Opinion. Stablon 12.5 Mg, Coated Tablet, Re-Assessment of Actual Benefit at the Request of the Transparency Committee. December 5, 2012.
[4]Emsley et al., 2018. *J. Clin. Psychiatry. 79* (4)
[5]Bonierbale et al., 2003. *Curr Med Res Opin.* 19(2):114-124
[6]Guelfi et al., 1989. *Neuropsychobiology. 22* (1), 41–48
[7]Invernizzi et al., 1994. *Neuropsychobiology.* 30 (2–3), 85–93
[8]Lepine et al., 2001. *Hum. Psychopharmacol.* 16 (3), 219–227
[9]Guelfi et al., 1992. *Neuropsychobiology.* 25 (3), 140–148.
[10]Lôo et al., 1992. *Br. J. Psychiatry. Suppl.* No. 15, 61–65.

TNX-601 ER Drug product

TNX-601 ER formulated with attention to FDA-guided potential abuse deterrent properties*

- The *only* abuse-deterrent properties approved for the labels of certain marketed opioids are extended-release formulations with physiochemical barriers +/- aversive components to abuse
- TNX-601 ER was formulated with attention to these potentially abuse deterrent properties:
  - Active ingredient, tianeptine oxalate less soluble than sodium salt, reducing extraction efficiency in solvents such as water and alcohol
  - Microcrystalline cellulose is a compression aid that results in extremely hard tablets, reducing ability to crush to fine particulate matter for insufflation or efficient extraction, pressed at >100 Newtons
  - Inclusion of high molecular weight gel-forming polymers also adversely affects the "syringe-ability" and injectability of the drug product
  - Inclusion of hydrophilic fumed silica as well as magnesium stearate may cause nasal irritation if insufflated; in high doses, orally ingested magnesium stearate may cause GI hyperactivity and irritation
  - All potentially serve to make TNX-601 ER a **non-optimal source of tianeptine for high dose abuse**

*https://www.fda.gov/drugs/information-drug-class/final-guidance-evaluation-and-labeling-abuse-deterrent-opioids

Summary: TNX-601 ER vs. Other Antidepressants

- Given tianeptine's unique metabolic pathway, which is independent of the hepatic P450 system, it is anticipated that, like tianeptine sodium, TNX-601 ER will have a reduced risk of drug-drug interactions compared to most antidepressants
- Unique mechanism of action (MOA) compared to available antidepressants in the U.S.
- The efficacy of tianeptine sodium IR is comparable to both selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressants[1,2] while being associated with a **low incidence of sexual dysfunction** compared with either of those classes[3], and **no associated derangement of sleep architecture, sedative effects, weight gain, or cognitive impairment[1]**
- Once-daily dosing regimen compared to tianeptine sodium IR at three times a day

[1]Wagstaff et al., 2001. *CNS Drugs.* 15(3), 231–259
[2]Kasper et al., 2002. *Eur Psychiatry.* 17 (Suppl 3), 331-340
[3]Bonierbale et al., 2003. *Curr Med Res Opin.* 19(2):114-124

Looking Forward: Additional Potential Indications for TNX-601 ER

Informed by clinical data and mechanistic insights

- Neurodegenerative disorders
  - Parkinson's (and associated conditions, e.g. depression and psychosis)[1]
  - Alzheimer's (and associated conditions, e.g. agitation, depression and psychosis)[2]
- ADHD[3]
- Stress disorders[4]
  - PTSD, Anxiety
- Aging/Neuroprotection[5,6]
  - Mild Cognitive Impairment
- Asthma[7]
- Overlapping chronic pain syndromes
  - Fibromyalgia[8]
  - Irritable bowel syndrome
- Addiction
  - Opiate use disorder[9]
  - Alcohol use disorder

[1]Levin, 2007. *Neurosci Behav Physiol.* 37(4):419-24
[2]García-Alberca et al., 2022. *J Alzheimers Dis.* 88(2):707-720
[3]Niederhofer et al., 2004. *Neuropsychobiology.* 49(3): 130-3.
[4]Krystal et al., 2009. *Drug Discov Today.* 14(13-14):690-697
[5]Yoo et al., 2015. *J Affect Disord.* 185:24-30.6
[6]Saiz-Ruiz et al., 1998. Prog. Neuro-Psychopharmacol. & Bio. Psychiat. 22(2): 319-329
[7]Lechin et al., 2004. *Methods Find Exp Clin Pharmacol.* 26(9): 697–701
[8]"ISRCTN16400909 – Tianeptine for the treatment of fibromyalgia: a prospective double-blind, randomised, single-centre, placebo-controlled, parallel group study". Controlled-trials.com. Archived from the original on 21 July 2010. Retrieved 13 August 2010
[9]Chu et al., 2010. *Behav Pharmacol.* 21(5-6):523-9


THANK YOU
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