Tianeptine - A Clinical Review.

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ABSTRACT

Depression is a wide spread disorder. The development of effective pharmacotherapy for major depression is important because it is such a widespread and debilitating mental disorder. The following review is based on the preclinical and clinical studies carried out on Tianeptine, an atypical antidepressant that lowers the adverse effects of stress on brain and memory. It is one of the many drugs being tested these days in the market as nootropics; it is presented as a "Smart Drug". These are believed to be of low-risk and work to improve, enhance, or repair damage done to the brain via injury or disease.

Keywords: Antidepressants, Antioxylic, Cognition enhancers, Neuroprotective, Nootropic

Introduction

Depression is a widespread, recurrent mental disorder that has detrimental effects on individuals, as well as society, at large. Although considerable progress has been made in characterizing the neurobiological squeals that result from this disorder, the factors that are responsible for depression's development and progression are not well understood. Research indicates that there is a heritable component to depression, and, more recently, investigators have identified candidate genes that appear to increase one's susceptibility for the disorder. This area of research has provided insight into the etiology of depression with the finding that gene polymorphisms interact with environmental factors, such as stressful events, to increase the likelihood that a person will develop major depression. For the past few decades, the prevailing view has been that depression results from abnormally low levels of monoamine neurotransmitter substances (e.g., serotonin, norepinephrine, dopamine), which is commonly known as the monoamine hypothesis. Support for this hypothesis was based on the incidental finding that efficacious antidepressants, such as monoamine oxidase inhibitors and tricyclics, increased monoamine neurotransmitter levels. Therefore, the primary focus of pharmacotherapy for depression has been to prescribe agents which are known to increase levels of the neurotransmitter serotonin, and today, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline, are the most prescribed pharmacological treatments for this disorder. Recent research suggests that increasing the levels of monoamines provides only an indirect contribution to antidepressant actions. Moreover, some findings are inconsistent with the monoamine hypothesis of depression, thereby suggesting that the neurochemical basis of the disorder is more

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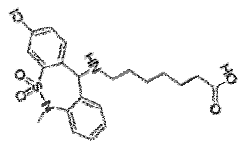
complicated than previously considered. For instance, traditional antidepressants reduce depressive symptoms only in a subset of patients, despite their low levels of monoamines, and are largely ineffective for people with severe forms of depression. In these latter cases, clinicians may resort to electroconvulsive shock therapy (ECT), which has proven to be one of the most effective treatments for severe, pharmacologically resistant forms of depression. Despite its effectiveness, however, ECT's mechanism of action remains largely unknown. An alternative and well-established treatment for depression is the drug Tianeptine, an antidepressant which does not share pharmacological properties with TCAs, MAOIs or SSRIs. Early studies suggested that tianeptine enhanced the uptake of serotonin, but more recent work indicates that tianeptine's actions as an antidepressant are independent of modulating serotonin levels. Instead, tianeptine'sprimary mode of action is to influence the expression of synaptic plasticity *via* the modulation of glutamatergic neurotransmission. Tianeptine's effectiveness in treating depression is of clinical, as well as conceptual, significance. That is, the contrast in mechanistic actions between SSRIs and tianeptine, combined with the observation that both types of agents can treat depression, serves as a challenge to the heuristic value of the monoamine hypothesis of depression.

It was discovered in the 1960s by the French Society of Medical Research as an SSRE (selective serotonin reuptake enhancer) for its antidepressant and antioxylic (anti-anxiety) qualities. In animal studies, it has been shown to prevent stress-induced morphological sequelae in the hippocampus and amygdala, as well as to prevent stress from impairing synaptic plasticity in the prefrontal cortex and hippocampus. It also has memory-protective characteristics, as it blocks the adverse effects of stress on hippocampus-dependent learning and memory.

Chemical structure of Tianeptine:



Pharmacokinetics:[1,2,3]

Table 1: Pharmacokinetic data Tianeptine [2]

Chemical Formula of Tianeptine	$C_{21}H_{25}ClN_2O_4S$
Molecular mass	436.953 g/mol
Bioavailability	99%
Plasma Protein binding	95%
Metabolism	Hepatic
Plasma half-life	2.5-3 hours, 4-9 hours (elderly)
Excretion	Renal (65%),Fecal (15%)

Tianeptine is a water-soluble nootropic, which can be administered orally [PO] or intravenously [I.V]. Volume of distribution is limited. [1] It does not undergo first-pass hepatic metabolism and has high bioavailability. It is not primarily metabolized by the hepatic cytochrome P450 system, indicating less likelihood of drug-drug interactions. [4,5] It is rapidly

eliminated by the kidneys. This rapid elimination makes adherence to dosage schedules very important. [**Illustrated in Table 1**]

Pharmacodynamics (Mechanism of action):

It has several potential mechanisms: It has a novel neurochemical profile.

- It increases Serotonin (5-hydroxytryptamine; 5-HT) uptake in the brain and reduces stress-induced atrophy of neuronal dendrites. It reduces stress on the brain, both physical and mental. It causes stress-induced alterations morphology and synaptic plasticity. As it alleviates stress, it also improved learning, brain cognition and memory, 2 things often diminished by serious depressive conditions.[4]
- It is thought to enhance the extracellular concentrations of Dopamine in selected brain and nerve/neuron pathways. It also speculated that Tianeptine works by modulating several types of Dopamine receptors within the brain. [5]
  Since Dopamine is a powerful mood boosting neurotransmitter, this can lead to profound effects.
- There even appears to be some effect on Glutamate receptors, which has an important part to play in reversing impaired neuroplasticity, which is often associated with stress.[6]
- Ithelps to treat depression and anxiety, which are currently believed to be due to its explicit effects stimulating both the AMPA (alpha-amino-3-hydroxy 5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate), and is believed to have memory protective properties.[2]
- It is a full agonist at the μ-opioid and δ-opioid receptors[13] with negligible effect at the κ-opioid receptors. Selective μ-opioid agonists typically induce euphoria, which may contribute to Tianeptine's antidepressant effect.[7]
- Possible anticonvulsant and analgesic activity of Tianeptine via immediate or downstream modulation of adenosineA_1 receptors (as the effects could be experimentally blocked by Adenosine receptor antagonists.[8]

Table 2: Comparison amongst side-effects of the antidepressants[1,2]

	SSRI	SSRE	TCAD
CVS	No	No	Yes
Sedative	No	No	Yes
Body weight/appetite-stimulation	No	No	Yes
Abuse potential	High	Low	Low
Cognitive impairment	No	No	Yes
Anticholinergic effects	No	No	Yes

Side effect and toxicity:

Unlike many antidepressants, Tianeptine has fewer negative side effects [**Illustrated in Table 2**]. The adverse effects associated are similar in many respects to those of the SSRIs and minimal in comparison with the tricyclic antidepressants.

Anticholinergic effects occur less often with Tianeptine than with tricyclic agents. [6]

Hepatoxicity is rare.

The dosage should be decreased in elderly patients and those with severe renal failure, but adjustment is not necessary in patients with alcoholism or hepatic impairment, or those undergoing haemodialysis.[8]

The side effects as mentioned below are minor and tolerable. They include: **Anticholinergic** [dry-mouth, constipation, urinary retention], **[α_1 blocking]** low blood pressure, **[H_1 blocking]** [8]

Table –3: Adverse effects classified according to their occurrence[9]

Common (>1% frequency)	
• Dizziness (up to 10%)	• Insomnia/nightmares (up to 20%)
• Drowsiness (up to 10%)	• Dry mouth (up to 20%)
• Constipation (up to 15%)	• Nausea
• Abdominal pain	• Weight gain (~3%)
• Agitation	• Anxiety/irritability
• Headache (up to 18%)	
Uncommon (0.1-1% frequency)	
• Flatulence	• Gastralgia
• Blurred vision	• Muscle aches
• Premature ventricular contractions	• Micturition disturbances
• Palpitations	• Orthostatic hypotension
• Hot flushes	• Tremor
• Bitter taste	
Rare (<0.1% frequency)	
• Hypomania	• Euphoria
• ECG changes	• Pruritus/allergic-type skin reactions
• Protracted muscle aches	• General fatigue
• Hepatitis	

Uses of Tianeptine:

- Major depression, depressed bipolar disorder, dysthymia [persistent mild depression] or adjustment disorder.[1]
- Benefits in regard to memory and learning abilities [3]
- It causes mood elevationcompared to the mood depreciating effects common with SSRIs. [3]
- In one study, it was found to be a logical treatment for Treatment Resistant Depression (TRD) [4]
- It has neuroprotective effects in the brain tissue [seen in rats exposed to a chronic stress model].[10]
- Used in Parkinson's diseaseand post-traumatic stress disorder (PTSD) where it is as safe and effective as Fluoxetine[SSRI] and Moclobemide [Selective MAO-A inhibitor].[11,12]
- In the treatment Irritable bowel syndrome. [Clinical trial has been conducted to

compare its efficacy and tolerability with Amitriptyline, showing it to be as effective as Amitriptyline and produced less prominent adverse effects such as dry mouth and constipation [Anticholinergic].

- Has been reported to be very effective for asthma.[13]
- Effective in men with depression and erectile dysfunction[14] [A 2005 study in Egypt]
- It is effective in treating pain due to fibromyalgia [clinical trial in Spain that ended in January 2007] [15]
- In the treatment of Attention-Deficit Hyperactivity Disorder [ADHD][17]
- Can have anticonvulsant and analgesic activity[18]

Dosage and frequency:

Onset of action:

Oral dose [**PO]**: Takes approximately between 2 to 6 weeks but some benefits have been reported to be observable within the first week of use. Pills formulation [**Capsule/ Tablet and Powder: 12.5 mg]**.The recommended dosage of capsules is usually 12-36 mg/day, taken as 12mg individual dosages, one in the morning,one in the afternoon and a final capsule/tablet in the evening.

Intravenously [I.V] injection by drug users in Russia, sold under the brand name "Coaxil") and is a Schedule III controlled substanceI.V administration reportedly causes an opioid-like effect and is sometimes used in an attempt to lessen opioid withdrawal symptoms. **Disadvantage of I.V route:** Often the solution is not filtered well and particles in the injected fluid block capillaries, leading to thrombosis and then severe necrosis. [3]

Biochemical Assay Tests:[18,19]

A study was conducted, in vivo extracellular unitary recordings, in vitro [3H]5-HT uptake and [3H] cyanoimipramine binding assays were used to assess the effect of acute and prolonged administration of the putative antidepressant tianeptine, on the 5-hydroxytryptamine (5-HT) transporter. Microiontophoretic application of tianeptine onto dorsal hippocampus CA3 pyramidal neurons, as well as its intravenous administration (2 mg/kg), increased their firing frequency. Following intracerebroventricular administration of 5,7-dihydroxytryptamine, the activation induced by the microiontophoretic application of tianeptine remained unchanged, thus suggesting that the 5-HT carrier is not involved in this effect. Furthermore, in spite of its activating effect on CA3 pyramidal neuron firing frequency, the intravenous administration of tianeptine did not alter the time of recovery of these neurons from microiontophoretic applications of 5-HT, an index of 5-HT uptake activity. In keeping with this observation, the acute administration of tianeptine did not change the effectiveness of the 5-HT reuptake blocker paroxetine (1 mg/kg, i.v.) in prolonging the suppressant effect of microiontophoretically-applied 5-HT. However, in rats that had received tianeptine for 14 days (20 mg/kg/day, S.C.), the recovery time from the suppressant effect of microiontophoretic applications of 5-HT was reduced by 40% and the effectiveness of paroxetine (1 mg/kg, i.v.) was decreased. These effects were no longer observed following a 48 h washout period. In a second series of experiments, the ability of tianeptine to interfere with the uptake blocking capacity of paroxetine was assessed in vitro, using hippocampal slices obtained from rats that had been treated with tianeptine for 14 days

(20 mg/kg/day, s.c.; by minipump). These were the result of the study to see the effect of acute and prolonged tianeptine administration on the 5-HT transporter: electrophysiological, biochemical and radioligand binding studies in the rat brain.

High-performance liquid chromatographic tests:

An improved analytical method for the quantitative measurement of tianeptine and its main metabolite MC_5 in human plasma was designed. Extraction involved ion-paired liquid–liquid extraction of the compounds from 1.0 ml of human plasma adjusted to pH 7.0. HPLC separation was performed using a Nucleosil C_{18}, 5 μm column (150×4.6 mm I.D.) and a mixture of acetonitrile and pH 3, 2.7 $g\,l^{-1}$ solution of sodium heptanesulfonate in distilled water (40:60, v/v) as mobile phase. UV detection was performed using a diode array detector in the 200–400 nm passband, and quantification of the analytes was made at 220 nm. [26]
For both tianeptine and MC_5 metabolite, the limit of quantitation was 5 $\mu g\,l^{-1}$ and the calibration curves were linear from 5 to 500 $\mu g\,l^{-1}$. Intra- and inter-assay precision and accuracy fulfilled the international requirements. The recovery of tianeptine and its metabolite from plasma was, respectively, 71.5 and 74.3% at 20 $\mu g\,l^{-1}$, 71.2 and 70.8% at 400 $\mu g\,l^{-1}$. The selectivity of the method was checked by verifying the absence of chromatographic interference from pure solutions of the most commonly associated therapeutic drugs. This method, validated according to the criteria established by the Journal of Chromatography B, was applied to the determination of tianeptine and MC_5-metabolite in human plasma in pharmacokinetic studies.[18]

Drug abuse and addiction potential:

Tianeptine is abused due to its anxiolytic properties. This is more commonly seen in people with pre-existing multisubstance abuse disorders.**Prevalence:** *141 cases of abuse were identified in France between 1989 and 2004, correlating to an incidence of 1-3 cases/1000 persons treated with Tianeptine and 45 cases between 2006 and 2011*. According to *Servier*, stopping treatment with Tianeptine is difficultas it may produce withdrawal symptoms. The severity of the withdrawal is dependent on the daily dose, with high doses being more difficult to quit. Singapore's Ministry of Health has restricted the use of tianeptine to psychiatrists due to its abuse potential, while Bahrain has classified it a controlled substance due to increasing reports of misuse and abuse by persons. In September 2012, France began treating Stablon as a controlled substance. Its use now requires a "secure prescription" form in France.[20,]

Future of Tianeptine:

This multitasking drug has a great deal of potential in medicine, therapeutic psychological and counseling goals, and provides a potential enhancement to brain function. It is one of the drugs that have found its way to improve the mental state of those suffering from debilitating disease and emotional conditions and is both effective, efficient, and has a limited amount of serious side effects. Hence Tianeptine may be a much safer alternative to many of the antidepressants on the market today. [22]

Conclusion:

Tianeptine is currently being used to treat depression, especially major depressive episodes, popularly in France and other countries throughout Europe. [19] It is able to improve mood and relieve feelings of stress, sadness, and anxiety. It is also noteworthy that it does not appear to cause any type of tolerance, addiction, or act as a sedative substance. [7] Furthermore, additional evidence shows that this drug may be helpful in treating issues like obsessive compulsive disorders [OCD], social anxiety, and even some eating disorders. The possibility even exists that it could lead to medications and treatments for neurodegenerative disorders like Alzheimer's disease, cerebral aging, and multiple sclerosis.[23,24]

References:

1. Zheng RKim B. Pharmacokinetic and bioequivalence assessment of two formulations of tianeptine sodium in healthy male volunteers. Int Journal of Clinical Pharmacology and Therapeutics. 2014;52(09):817-823.
2. Wagstaff A, Ormrod D, Spencer C. Tianeptine. CNS Drugs. 2001;15(3):231-259.
3. Carlhant D, Garrec J, Guedes Y, Salvadori C, Mottier D, Riche C. Pharmacokinetics and Bioavailability of Tianeptine in the Elderly. Drug Invest. 1990;2(3):167-172.
4. Brink C, Harvey B, Brand L. Tianeptine: A Novel Atypical Antidepressant that May Provide New Insights into the Biomolecular Basis of Depression. PRN. 2012;1(1):29-41.
5. Uzbay T. Tianeptine: Potential influences on neuroplasticity and novel pharmacological effects. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008;32(4):915-924.
6. Waintraub L, Septien L, Azoulay P. Efficacy and Safety of Tianeptine in Major Depression. CNS Drugs. 2002;16(1):65-75.
7. Berridge Kringelbach M. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology. 2008;199(3):457-480.
8. Uzbay L, Kayir H, Ceyhan M. P.6.025 Tianeptine inhibits pentylenetetrazole-induced seizures in mice via adenosinergic receptors. European Neuropsychopharmacology. 2004;14:S367.
9. McEwen BChattarji S. Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine. European Neuropsychopharmacology. 2004;14:S497-S502
10. McEwen BOlié J. Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. Molecular Psychiatry. 2005;10(6):525-537.
11. Defrance, R; Marey, C; Kamoun, A. Antidepressant and anxiolytic activities of tianeptine: an overview of clinical trials. Clinical Neuropharmacology. 2011 Suppl (2): S74–82.
12. Kasper SMcEwen B. Neurobiological and Clinical Effects of the Antidepressant Tianeptine. CNS Drugs. 2008;22(1):15-26.

13. Lechin F, van der Dijs B, Lechin A. Treatment of bronchial asthma with tianeptine. Methods and Findings in Experimental and Clinical Pharmacology. 2004;26(9):697.

14. ElShafey H, Atteya A, Abu elMagd S, Hassanein A, Fathy A, Shamloul R. ORIGINAL RESEARCH—ERECTILE DYSFUNCTION: Tianeptine Can Be Effective in Men with Depression and Erectile Dysfunction. The Journal of Sexual Medicine. 2011;3(5):910-917.

15. Önder E, Tural Ü, Aker T. A comparative study of fluoxetine, moclobemide, and tianeptine in the treatment of posttraumatic stress disorder following an earthquake. European Psychiatry. 2006;21(3):174-179.

16. Baune BRenger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression – A systematic review. Psychiatry Research. 2014;219(1):25-50.

17. Aleksandrovskiĭ, IuA; Avedisova, AS; Boev, IV; Bukhanovkskiĭ, AO; Voloshin, VM; Tsygankov, BD; Shamreĭ, BK , Efficacy and tolerability of coaxil (tianeptine) in the therapy of posttraumatic stress disorder.(Year 2005) 105 (11): 24–9.

18. Piñeyro G, Deveault L, Blier P, Dennis T, de Montigny C. Effect of acute and prolonged tianeptine administration on the 5-HT transporter: electrophysiological, biochemical and radioligand binding studies in the rat brain. Naunyn-Schmiedeberg's Archives of Pharmacology. 1995;351(2):111-118.

19. Gaulier J, Marquet P, Lacassie E, Desroches R, Lachatre G. High-performance liquid chromatographic determination of tianeptine in plasma applied to pharmacokinetic studies. Journal of Chromatography B: Biomedical Sciences and Applications. 2000;748(2):407-414.

20. Gassaway M, Rives M, Kruegel A, Javitch J, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Translational Psychiatry. 2014;4(7):e411.

21. Levin O. Coaxil (tianeptine) in the treatment of depression in Parkinson's disease. Neuroscience and Behavioral Physiology. 2007;37(4):419-424.

22. Sohn W, Lee O, Kwon J, Park K, Lim Y, Kim T et al. Tianeptine vs amitriptyline for the treatment of irritable bowel syndrome with diarrhea: a multicenter, open-label, non-inferiority, randomized controlled study. Neurogastroenterology & Motility. 2012;24(9):860-e398.

23. Niederhofer H. Tianeptine as a Slightly Effective Therapeutic Option for Attention-Deficit Hyperactivity Disorder. Neuropsychobiology. 2004;49(3):130-133.

24. Voican C, Corruble E, Naveau S, Perlemuter G. Antidepressant-Induced Liver Injury: A Review for Clinicians. American Journal of Psychiatry. 2014;171(4):404-415.

25. Zoladz P, Park C, Munoz C, Fleshner M, Diamond D. Tianeptine: An Antidepressant with Memory-Protective Properties. Current Neuropharmacology. 2008;6(4):311-321.