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Tianeptine: an atypical antidepressant with multimodal pharmacology

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Abstract

Background: Tianeptine is an atypical antidepressant marketed as Stablon since the late 1980's. While chemically very similar to tricyclic antidepressants, tianeptine was thought to have the apparently paradoxical mechanism of action of enhancing serotonin reuptake. However, recent data highlight a multimodal pharmacology for tianeptine including actions at glutamatergic synapses (inhibiting NMDA receptors and an indirect effect on AMPA receptors) coupled with agonist effects at mu opioid receptors (μ-receptors). **Objective:** We have reviewed clinical and preclinical data for tianeptine to provide a comprehensive study of its pharmacology. **Results:** Clinical trials show that tianeptine is at least as efficacious as first-line antidepressant treatments, with improved tolerability as it is significantly less prone to disrupting the patient's normal functionality. Tianeptine appears more efficacious in males than females, although these gender-specific differences may be accounted for by pharmacokinetics. Preclinical data suggest that the ability to stabilise glutamatergic neurotransmission may underlie tianeptine's ability to improve cognitive function and anxiety-related symptoms. Alternatively, μ-receptor activation of the mTOR signalling pathway could lead tianeptine to be a fast-acting antidepressant. Agonist actions at μ-receptors could also explain the potential abuse liability and dependence issues seen with high dose tianeptine. **Conclusion:** Tianeptine itself is off patent, but it still holds much promise as an experimental tool yielding valuable insights into the molecular mechanisms underlying depression.

1. Introduction

Major depressive disorder (MDD) is a highly pervasive disorder, characterised by persistent low mood, low self-esteem and anhedonia. In the UK, depression affects 4 million adults, 8.4% of the total population and has been linked with poor health, significant comorbidity and mortality [1-3]. MDD, therefore, is characterised as a severely debilitating disease with a major impact not only on a person's quality of life but can also place a massive financial strain on a country's healthcare system.

The prevalence of the monoamine hypothesis as a causative factor of depression has driven the development of therapies that aim at restoring the neurochemical imbalance in noradrenaline, serotonin and dopamine. The principle classes of antidepressants utilised to restore this neurochemical alteration are the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs).All four classes of antidepressants have proven to be catalysts by dramatically improving the quality of life of depressed patients [4]. These agents, however, are associated with limitations in their onset of action, efficacy, tolerability and safety. These antidepressants have a delayed time of onset as they usually take four to six weeks to exhibit a therapeutic benefit [5]. Problems with the efficacy of antidepressant therapy include drug resistance where between one and two-thirds of patients will not respond to the first antidepressant prescribed and 15 to 33 percent will not respond to multiple interventions [6-7]. In terms of tolerability, antidepressants that interfere with the serotonin system can lead to emotional detachment [8] and interfere with normal sexual function [9] thus discouraging patients from complying with therapy. Finally, in terms of safety, even though antidepressants are generally regarded as safe, they have been associated with life-threatening side-effects including cardiovascular effects [10] and, controversially, an increased risk of suicide [11-12].

Tianeptine is an atypical antidepressant with a novel mechanism of action. Marketed since the late 1980's as Stablon, tianeptine is available in Europe, Latin America, and Asia as a treatment for MDD although it is not available in the UK or North America [13]. Here we review the evidence demonstrating the clinical efficacy and potential advantages of tianeptine as an antidepressant, alongside recent advances in understanding its unique

multimodal psychopharmacology which could shed light on the molecular mechanisms underlying depression.

2. Clinical Efficacy of Tianeptine

We have attempted a comprehensive review of all the accessible clinical trial information on tianeptine and our findings are summarized in Table 1. The clinical efficacy of tianeptine has been assessed in a vast number of clinical trials, including two small term placebo controlled double blind studies; their purpose being the assessment of the efficacy of tianeptine in adult patients of both genders with unipolar or bipolar depression [14-15]. Treatment of both male and female patients (n=129) with tianeptine (37.5 mg/day) for 42 days resulted in a reduction in the Montgomery-Asberg depression scale (MADRS) of 62.3% as compared to placebo (48.5%) [14].The efficacy of tianeptine has also been shown in long-term studies to assess remission and relapse. In one study, 286 adult patients of both genders were treated with tianeptine for 6 weeks [16]. The patients that responded to tianeptine (n=185) were then randomly assigned to tianeptine (37.5 mg/day, n=111) or placebo (n=74) for up to 18 months and were assessed for their rate of relapse and reoccurrence by using the Hamilton depression rating scale and the CGI scale [16]. The results of the trial revealed that by the 18-month timepoint, in tianeptine treated patients, the rate of relapse and reoccurrence was lower (16%) compared to placebo (36%) [16].

Most of the clinical studies investigating the antidepressant efficacy of tianeptine have compared its efficacy in parallel with other classes of antidepressants. In double-blind studies of 4-24 weeks duration, tianeptine (37.5mg/day) showed similar efficacy as the TCAs amitriptyline (75 mg/day) [17-18] and imipramine (150 mg/d) [15], the atypical antidepressant mianserin (60mg/day) [19] but also the SSRIs fluoxetine (20mg/day) [20] and paroxetine (20mg/day) [21]. Additionally, in a meta-analysis comparison with SSRIs, tianeptine was shown to be just as efficacious during the same treatment period of 6 weeks [22].

Clinical evidence also supports an improvement in cognitive function following treatment with tianeptine. A 42-day study was performed as a double-blind, controlled trial and it utilised hospitalised adult patients that were classified using the DSM-IV criteria as having major depression or bipolar disorder [23]. For the purposes of the study, adult patients of both genders were treated in parallel either with tianeptine (37.5 mg/d) or paroxetine (20mg/d) and were assessed for improvement in cognitive function [23]. The investigators reported that both antidepressants significantly boosted cognitive function by improving alertness, selective attention and problem solving [23]. Interestingly, they also reported that patients treated with tianeptine showed greater improvement in cognitive function, an observation, however, that did not reach statistical significance [23]. In a separate study of MDD patients treated with either tianeptine (37.5 mg/d) or escitalopram (10 mg/d) for 12 weeks, both drugs improved subjective cognitive impairment of memory and concentration [24] Furthermore, these authors showed that tianeptine led to more improvements in neurocognitive functions, especially in commission errors and verbal immediate memory, compared with escitalopram [24].

In addition to its anti-depressive properties, tianeptine has been suggested to exhibit anxiolytic effects. In adult depressed patients that had concomitant anxiety [19], tianeptine (37.5 mg/day) was shown to result in an approximately 52% reduction in anxiety scores as assessed by the MADRS [19]. Several studies of between 4-24 weeks have demonstrated that the anxiolytic profile of tianeptine is similar to that of amitriptyline [17-18] mianserin (60mg/day) [19] , fluoxetine (20mg/day) [25] and paroxetine (20mg/day) [21] and even the benzodiazepine alprazolam (1.5mg/day) [19]. Other studies suggest that tianeptine is superior to fluoxetine at relieving anxiety; patients on tianeptine required 50% less concomitant anxiolytic treatment than fluoxetine-treated patients [25]; this suggests that tianeptine is more effective at relieving anxiety associated with depressive illness than the SSRI fluoxetine and possible other antidepressants of the same class. The ability of tianeptine to effectively treat anxiety symptoms in MDD patients may be related to its ability to improve neurocognitive deficits [26].

There is also strong clinical evidence that tianeptine is beneficial for overcoming treatment-resistant depression when combined with other antidepressants [27-28]. Specifically, in one study, this concept was tested in an open-label, prospective, multicentre 6-weeks study that included 150 adult patients of mixed genders [27]. Patients were diagnosed with MDD and did not respond or partially responded to SSRI monotherapy [27]. The result of

the study revealed that 65% of the enrolled patients responded to a combination treatment with low dose of tianeptine (≤ 37.5 mg/day) and around 40% of patients went into remission as defined by both the MADRS and Hamilton Depression Rating Scale (HDRS) [27]. Furthermore, the investigators reported that a combination with high doses of tianeptine (≥ 37.5 mg/day) produced a fourfold increase in the probability of the patients going into remission, as defined by HDRS, at the study end point; when patients were assessed using the MADRS there was a twofold increase in the probability [27].

Finally, an interesting observation concerning the clinical efficacy of tianeptine is its tendency to exhibit gender-specific differences. In the study by Nickel et al. [23] comparing paroxetine with tianeptine, the authors concluded that both antidepressants were effective at reducing depressive symptoms in both genders, however, males had a greater response on tianeptine while females on paroxetine. Additionally, the gender-specific differences of tianeptine have been reported in a small trial involving 38 depressed adult patients of both genders [29]. This study compared the efficacy of tianeptine (37.5mg) vs paroxetine (20mg) with regard to their effects on sleep regulation [29]. The results showed that tianeptine was more effective at improving sleep pattern in males compared to females.

Overall, tianeptine has well established clinical efficacy as an antidepressant; better than placebo and at least equivalent to first-line treatments (Table 1). The improvement in depression scores in MDD patients is also associated with an improvement in anxiety symptoms and in cognitive abilities. In terms of time of onset or rate of relapse to depressive episodes, tianeptine's abilities are not conclusively better than other antidepressants [13]. Tianeptine may have the advantage of being better tolerated than other antidepressants.

2.1 Safety and Tolerability of Tianeptine

A number of safety studies from various clinical trials have described tianeptine as a well-tolerated drug. The side effect profile of tianeptine is mostly associated with gastrointestinal disturbances such as nausea, constipation and abdominal pain but also with unwanted CNS effects including headaches, dizziness, and change in dream patterns [30]. Interestingly in a double-blind trial, the tolerability of tianeptine was superior to that of paroxetine where the incidence of dropout, due to side effects, was significantly lower (19

vs 6) [21]. Comparison of tianeptine with TCAs and MAOIs has yielded the same superiority in tolerability; tianeptine lacks the serious adverse effects on the cardiovascular and cholinergic system associated with these classes of antidepressants, leading to much less impairment on sleep, arousal, cognition, weight gain or psychomotor functioning [31]. Additionally, unlike MAOI, tianeptine lacks the life-threatening drug interactions [31]. Tianeptine's safety credentials are furthermore enhanced by the fact that it has a very low overdose risk, therefore, has been classed as a drug with a low abuse potential. Surprisingly in a single case study, a patient abused tianeptine by consuming 50 times the recommended dose on a daily basis and no severe toxicity was observed [32].

Undoubtedly, one of the major drawbacks of current antidepressant treatments is the discontinuation symptoms that occur after cessation of treatment. In most cases this discontinuation syndrome is short-term and has no major impact on a person's quality of life; however in other cases, it may last longer and symptoms may interfere with normal functioning [33]. Tianeptine is one of the few, if not the only, antidepressant that has not been associated with a discontinuation syndrome. In an open study evaluating the safety of tianeptine in 1,858 patients in general practice, stopping the antidepressant was not associated with withdrawal or discontinuation symptoms [34].

Individuals suffering from MDD are associated with a high prevalence of sexual dysfunction. A French study involving 4557 outpatients concluded that the prevalence of sexual dysfunction was 35% for spontaneously reported problems and 69% for problems identified by physician questioning [35]. Antidepressant therapy is clinically proven to aggravate such problems; results from the same study revealed that patients on antidepressants increased the frequency of sexual dysfunction compared to the untreated patients [35]. However, this exacerbation is less frequent with tianeptine. In comparison with TCAs and SSRIs, tianeptine exhibited a lower incidence of sexual dysfunction having a similar rate of untreated patients [35]. Not only is tianeptine associated with decreased frequency of sexual dysfunction but it is shown to be beneficial in men with depression with erectile dysfunction. In a randomised, double-blind, placebo-controlled, crossover trial involving 68 male patients, tianeptine significantly improved their erection when compared with males on placebo [36].

3. Neurobiological Effects of Tianeptine

3.1 Brain Structure and Neurotrophic Effects

Neuroplasticity is the ability of the adult and differentiated brain to adapt functionally and structurally to internal and external stimuli [37]. There are three main brain regions which undergo neuroplastic adaptation and are assumed to be affected during MDD; these regions are the hippocampus, the amygdala and the prefrontal cortex [38] which are responsible for controlling emotion, perceptions and contribute to cognitive function. It is believed that during MDD these regions undergo alterations in volume, reduction in neuronal size and density, decreased adult neurogenesis and glial density [39-42]. Specifically, a study involving 16 patients with depression revealed that in all cases the volume of the left side of the hippocampus was 19% smaller when compared to 16 non-depressed patients [41]. In the amygdala, it has been suggested that during reoccurring episodes of depression the core amygdala volume is reduced [40], however following a first episode of depression the total amygdala volume is increased [42]. Finally, the prefrontal cortex has been associated with decreased volume of the grey and white matter [41,43].

Treatment with tianeptine has proven to be successful at reversing the alterations on brain structure and plasticity induced by chronic depressed and stress states. Specifically, this has been shown in a study performed on tree shrews that had been subjected to psychosocial stress, receiving chronic administration with tianeptine (50mg/kg) over the span of 28 days [44]. Tianeptine administration potentiated proliferation of dentate gyrus precursor granule cells and restored hippocampal volume [44]. A different study showed that tianeptine not only normalised the rate of proliferation but was also able to decrease cellular apoptosis in the hippocampus [45]. Tianeptine has also been shown to be effective in reversing stress-induced atrophy; treatment of male Sprague-Dawley rats with tianeptine prevented and reversed dendritic atrophy of hippocampal CA3 pyramidal neurones [46]. These effects of tianeptine may be mediated by increases in neurotrophic factors. Chronic treatment with tianeptine increased levels of brain-derived neurotrophic factor in the hippocampus and prefrontal cortex of rats [47].

3.2 Synaptic Plasticity

Synaptic plasticity is the ability of neurones to undergo activity-dependent alterations in synaptic function in order to determine how the synapse will respond to afferent activity [48]. Altered synaptic function and plasticity have been implicated in the pathophysiology of depression with abnormal synaptic plasticity in the regions of the hippocampus, amygdala and prefrontal cortex [49]. More specifically the use of animal models has revealed that acute and chronic stress inhibits the ability of the hippocampus and the prefrontal cortex to undergo long-term potentiation (LTP) [50-51]. In the amygdala, the opposite scenario is observed where acute and chronic stress potentiates LTP instead of inhibiting [51].

Preclinical data involving tianeptine have shown its beneficial effects in reversing alterations in plasticity. Tianeptine (10mg/kg) successfully enhanced synaptic function in the hippocampus [52-53] and prefrontal cortex [53] while maintaining normal synaptic function in the amygdala [54] of male Sprague-Dawley rats; the potentiation of LTP was reported to occur immediately after tianeptine administration. Interestingly tianeptine reversed the inhibitory effects of stress on LTP and mediated generation of a form of low threshold potentiation known as burst potentiation (PBP) [53-54]; priming of PBP was independent of stress experience. Tianeptine had no impact on amplification of LTP in the basolateral nucleus of the amygdala following a stressful stimulus [54].

3.3 Memory and Cognition

A functional consequence of MDD and stress involves impairment of cognitive and memory function. Impairment in memory function is believed to occur due to damage to the hippocampus by stress and its related hormones [50, 55]; particularly damage in the region is associated with altered spatial memory. Tianeptine has been shown to improve memory function in several experiments. For instance, in the radial-arm water maze, tianeptine (10mg/kg) prevented stress-induced impairment of rat spatial memory brought about by exposure to a predator [56]. Fascinatingly, evidence from the same experiment suggests that tianeptine improves memory without affecting the stress-induced rise in glucocorticoid suggesting that tianeptine does not interfere with activation of the hypothalamic-pituitary-adrenal axis following stress [56]. These effects of tianeptine are consistent with findings obtained from adrenalectomised rats [55].

Unlike the hippocampus which is responsible for spatial memory, the amygdala plays a crucial role in the acquisition and storage of emotional memories. During MDD the

amygdala is thought to be dysregulated, with fear-related learning being impaired [57-58]. Specifically, it is hypothesised that the amygdala exhibits potentiation of synaptic function and LTP during intense emotional experiences [59-60] resulting in amplification of fear-related behaviour. In animal models of emotional learning, tianeptine has been shown to be effective in preventing stress-induced enhancement of the amygdala. In more detail, administration of tianeptine (10mg/kg) reduced auditory fear conditioning in rats; the authors report that these effects of tianeptine are observed after long-term administration and not acutely [61].

4. Psychopharmacology of Tianeptine
4.1 Actions at the Serotonin Reuptake Transporter

One molecular target of tianeptine is the serotonin reuptake transporter (SERT) – a transporter which mediates reuptake of serotonin in neurones [62]. The majority of clinically available antidepressants are SERT inhibitors, they bind to an allosteric site on SERT decreasing its activity [62-63]. SSRIs have been proposed to inhibit SERT by interacting with the C-terminal part of SERT containing the transmembrane domains 10 and 12; specifically they form dipole-dipole interactions or hydrogen bonds with the benzene ring of the Tyr95 and make the transporter adopt a conformation that decreases the affinity for serotonin or reduces its rate of transport [62-63].

Tianeptine is chemically somewhat similar to tricyclic antidepressants, comprising of a core 3-chlorobenzothiazepine nucleus, and thus it exerts similar molecular behaviour in that it binds at the same allosteric site of SERT [64]. However, a major difference between TCAs and tianeptine is the presence of the amino heptanoic acid on C3; the presence of which gives tianeptine SERT enhancing properties [64]. This side chain is thought to lock the transporter in a conformation which increases affinity and reuptake (V_{max}) of serotonin [65]. Therefore, unlike SERT inhibiting antidepressants, tianeptine is defined as a positive allosteric modulator of SERT or a serotonin reuptake enhancer. Early binding studies indicated that tianeptine was selective for SERT as it did not bind to receptors for serotonin, dopamine, glutamate, GABA, acetylcholine, noradrenaline or histamine nor did it affect the transporters for noradrenaline or dopamine [66-67].

Similarly to other classes of antidepressant, tianeptine was anticipated to interfere with neurotransmission of the serotonin system, due to its apparent mechanism of action. Initially, this notion was shown to be true by experiments that revealed that acute and sustained administration of tianeptine (10mg/kg) decreased the synaptic availability of serotonin in rat brains [66, 68]. Additionally, administration of tianeptine was shown to decrease both the number and mRNA levels of SERT sites in the dorsal raphe nucleus of rat brain [69]. However, the validity of these studies has been questioned due to the technical limitations that could not be avoided at the time [70]. More recent studies performed on the corticolimbic structures of rats suggest that acute/chronic treatment with 10 mg/kg tianeptine has a negligible effect on synaptic serotonin levels [70]. Electrophysiological studies on rat dorsal raphe nuclei revealed that sustained administration of 20mg/kg/day tianeptine did not alter the firing rate of serotonin neurons. Moreover, prolonged treatment with tianeptine did not impact on the activity of postsynaptic serotonin 1A receptors or the activity of presynaptic serotonin autoreceptors [71]. Additionally, the antidepressant effects of tianeptine have been shown to be potentiated after enhanced serotonergic transmission via the use of fluoxetine [72]. Collectively the results have led to the notion that direct serotonin system modulation is unlikely to be the mechanism of antidepressant efficacy of tianeptine. However, these findings do not preclude the possibility that clinically tianeptine modulates serotonin function since the doses used in these preclinical studies may not translate directly to clinical dosing.

4.2 Glutamatergic Mechanisms Underlying Cognitive and Synaptic Effects of Tianeptine

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system playing a crucial role in many aspects of brain function including neuronal regeneration, dendritic branching and learning and memory behaviours [73-74]. Disturbances in glutamate signalling have been linked with mood disorders [75-76]. For example, changes in glutamate levels have been observed in the cerebrospinal fluid, brain tissue and plasma of individuals with mood disorders and suicide victims [77-78].

I*n vitro* and *in vivo* studies have shown that tianeptine normalises disrupted glutamatergic neurotransmission in the hippocampus and the amygdala. In rodents, during MDD and stress conditions, there is an increase in extracellular glutamate levels in the amygdala [79] and the hippocampus [80]. In the hippocampus, glutamate overactivity is associated with a decrease in neuronal size, density and ultimately volume [81]. This process is thought to be mediated via the mechanism of excitotoxicity [82]. Conversely, glutamate is thought to enhance amygdala function by inducing dendritic hypertrophy in the basolateral nucleus [83].Treatment with tianeptine has been associated with downregulation of the glial glutamate transporter GLUT-1 mRNA in the hippocampus of chronic restrained mice which is the hallmark of decreased glutamate levels. Additionally, tianeptine (10mg/kg) has been shown to inhibit the stress-induced increase in NMDA channel currents [84]. Stress-induced increases in extracellular glutamate in the amygdala were inhibited by tianeptine, but not by fluoxetine [79]. More recently, an in vivo microdialysis study in rats subjected to repeated stress showed that tianeptine inhibited downregulation of vGLUT2 expression in the amygdala, downregulation of which indicates impairment of amygdala glutamate neurochemistry [85]. In the same study daily treatment of tianeptine was shown to modify glutamatergic tone in non-stressed control rats by enhancing vesicular localisation of SNAP-25.

While tianeptine appears to stabilise the glutamatergic signalling, it also has effects on the ionotropic glutamate receptors. While both NMDA and AMPA receptors are crucial for the normal functioning of neurones, overstimulation of NMDA receptors leads to excitotoxicity while AMPA receptors do not [86]. It has been shown that antagonists of the NMDA receptor complex and positive modulators of AMPA receptors exhibit antidepressant-like effects in animal models [87]. Tianeptine is thought to perturb NMDA receptor function while it potentiates the function of AMPA receptors. Chronic administration of tianeptine (10mg/Kg/day) is associated with changes in the amplitude ratio of NMDA receptors to AMPA/kainate receptor-mediated currents that are altered during stress in CA3 hippocampal neurone [84]. The mechanism by which tianeptine produces this dual effect upon the glutamate system may result from an interaction with the glycine allosteric site on NMDA receptors. Glycine facilitates excitation at NMDA receptors to varying extents depending on the NMDA receptor subunit composition. In mice, an antagonist of the glycine site on the NMDA receptor enhanced the antidepressant-like effects of tianeptine in the forced swim test, while D-serine blocked tianeptine's effects [88]. These authors also showed that the AMPA receptor blocker NBQX reduced tianeptine's antidepressant-like

effects [88]. Assuming that tianeptine does indeed interfere with the function of NMDA receptors this would result in the prevention of overactivation of the receptors thus preventing excitotoxicity but could also potentiate AMPA mediated signalling by inhibiting GABAergic neurotransmission via the action of NMDA receptors present in GABAergic interneurons [89]. The AMPA-related function is also thought to be enhanced via an action upon mTOR signalling.

The mammalian/mechanistic target of rapamycin (mTOR) is an atypical serine/threonine kinase implicated in various neuronal functions including inducing neurogenesis, axonal sprouting and dendritic spine growth [90]. Emerging research into the mechanisms of action of ketamine, a fast-acting glutamatergic antidepressant, have highlighted the potential role of mTOR signalling in depression and in antidepressant responses [91]. Activation of AMPA and NMDA receptors results in the activation of the mTOR signalling cascade which in turn initiates various neurophysiological processes [91]. In addition, the mTOR pathway positively regulates the glutamatergic system by increasing the expression and release of BDNF which acts upon theTrkB receptors which in turn increase the translation and trafficking of AMPA receptors on the cell membrane of neurons [91]. Preclinical studies utilising animal models of depression have reported decreased mTOR activation in the amygdala [92], PFC [93] and hippocampus [94]. Interestingly, in a recent paper it has been shown that in rat primary hippocampal neurones that have been exposed to toxic conditions, tianeptine reversed the structural abnormalities caused by stimulating dendritic outgrowth, spine density, and synaptic proteins and these effects were directly correlated with activation of the mTOR complex 1 (mTORC1) pathway [95].

The actions of tianeptine on mTOR signalling could explain tianeptine's fast-acting antidepressant-like actions in animal models. Ketamine, for example, is a non-selective NMDA receptor antagonist which at low doses (10mg/kg) has been shown to have a potent antidepressant response in animal models of depression and this response is thought to be mediated by rapid activation of the mTOR signalling pathway [69]. Interestingly, ketamine has been shown to rapidly increase synapse spine formation, an effect which is mediated by increasing the levels of the postsynaptic proteins PSD95 and GluR1 and the presynaptic protein synapsin [97]. The process of synapse formation following ketamine administration was inhibited following ICV infusion of rapamycin, an mTOR-selective inhibitor, which also blocked the antidepressant effects of ketamine. Based on these findings ketamine is thought to produce its fast-acting responses by direct

activation of the mTOR signalling pathway (a process mediated via the enhancement of AMPA-mediated signalling) which results in spontaneous and sustained elevation of synapse-related proteins and therefore increase in synapse formation. Compared to ketamine, classic antidepressants which act upon monoamine signalling have also been shown to enhance mTOR signalling, however, they do not do this via a direct action upon the pathway and this is the reason why they are thought to take weeks to produce their antidepressant-response [98]. Thus tianeptine, which appears to also modulate mTOR signalling, as it enhances AMPA-related signalling, could elicit rapid antidepressant responses via this mechanism.

4.3 Interactions with μ-receptors

Clinically, recommended dosing with tianeptine is 37.5 mg/day. At high doses (75 up to 3000 mg/day) tianeptine has been reported to be associated with a risk of abuse and dependency [99-106]. For example, Kisa et al [103] reported that a 34-year-old patient developed tianeptine dependence after using doses of 750 mg/day of tianeptine for one year. Evidence also suggests that tianeptine dependence is likely to develop in patients with substance dependence [99-101, 104]. Furthermore, it has been reported that a mother using 650 mg per day, and her newborn baby, were dependent on tianeptine [106]. The newborn baby suffered from neonatal abstinence syndrome after delivery and was successfully treated with morphine and urine drug screen was negative for both the mother and newborn [106].

This is perhaps not surprising in light of preclinical studies demonstrating that tianeptine can increase dopamine release; an effect associated with euphoria and the rewarding properties of drugs of abuse [108]. In rats, tianeptine at 5 mg/kg increased extracellular dopamine levels in the nucleus accumbens and at higher doses (10mg/kg) in the striatum and frontal cortex [109, 110]. These effects were independent of any serotonin mediated actions of tianeptine [109] and could account for the apparent abuse and dependency seen at higher doses of tianeptine.

Ari et al [107] reported that naloxone (a non-selective opioid receptor antagonist) was effective in the treatment of amitriptyline and tianeptine poisoning in a 33-year-old woman with respiratory arrest and signs of opioid poisoning. These authors suggested that the high dose tianeptine and amitriptyline interacted with opioid receptors since naloxone effectively reversed these effects. Interestingly, analgesic effects of tianeptine have been

reported where 10 mg/kg produced a significant increase in reaction time on tail-flick latency or hot-plate in mice [111]. These authors suggested that tianeptine's effects were mediated via an interaction with serotonin since inhibiting biosynthesis blocked the analgesic actions of tianeptine. However, it has also been reported that the combination of morphine with tianeptine significantly decreased morphine antinociceptive tolerance and suppressed the incidence of naloxone-precipitated withdrawal symptoms in mice [112].

Tianeptine's action at opioid receptors has recently been demonstrated using radioligand binding and functional cell-based assays [113]. Tianeptine has been shown to bind and act as a μ-receptor agonist (K_i (human) 383 ± 183 nM; EC_{50} (human) 194 ± 70 nM; EC_{50} (mouse) 641 ± 120 nM), a lower efficacy delta-opioid receptor (δ-receptor) agonist (EC_{50} (human) 37.4 ± 11.2 μM; EC_{50} (mouse) 14.5 ± 6.6 μM) and inactive at the kappa-opioid receptor (κ-receptor) [113]. These authors also demonstrated that tianeptine has no agonist or antagonist activity at metabotropic glutamate receptors. They further proposed that the activation of μ-receptor signalling by tianeptine could trigger dopamine release which may be responsible for the modulation of the glutamatergic system; dopamine acting at presynaptic dopamine receptors on glutamatergic presynaptic terminals could enhance glutamate signalling. Such a mechanism could account for the corrective effect of tianeptine on increased NMDA receptor signalling in stressed animals [115].

Activation of μ-receptors could explain the potential abuse liability and dependence issues seen with high dose tianeptine. However, activation of both μ- and δ-receptors could also contribute to the antidepressant actions of tianeptine. Opiates have been used historically as antidepressants and opioid receptors are increasingly recognised to play a role in the regulation of mood and emotional behaviours [115-116]. For example, the partial μ-receptor agonist buprenorphine, which also has κ-receptor antagonist properties, has antidepressant effects in patients and antidepressant-like activity in mice [117-119]. Indeed the acute and chronic antidepressant-like behavioral effects of tianeptine have recently been shown to require the μ-receptor using μ-receptor deficient mice [120]. Furthermore, the hypophagic, analgesic, hyperactive and conditioned place preference effects of tianeptine were all dependent on the μ-receptor [120]. Interestingly, one downstream effect of μ-receptor activation is regulation of mTOR signalling [121]. Tianeptine's μ-receptor agonist properties [113] could lead to enhanced AMPA-related signalling since it promotes

mTOR activation which in turn increases the translation and trafficking of AMPA receptors in neurones.

5. Pharmacokinetics of Tianeptine

In healthy individuals, the pharmacokinetic properties of tianeptine have been extensively studied. Once in the gastrointestinal tract, tianeptine is rapidly absorbed and has a high bioavailability (90%) [122]. The absorption of tianeptine is modestly influenced by food intake, with both the time to reach maximum concentrations and lower peak concentrations increasing by 0.5h and 25% respectively [123]. Once in the blood stream, tianeptine becomes highly (95%) bound to the plasma protein human serum albumin; this aspect is associated with tianeptine's poor volume of distribution [122]. In addition, tianeptine also exhibits saturable binding to the α1-acid glycoprotein [125]. Once in the blood stream, tianeptine is primarily metabolised by hepatic enzymes and undergoes β-oxidation of its heptanoic side-chain leading to the generation of two major metabolites; MC5 and MC3 [122]. Only MC5 is known to possess pharmacological activity [124]. Indeed, MC5 has been shown to elicit μ-receptor dependent antidepressant behavioural effects comparable to tianeptine [120].

Tianeptine shows rapid elimination from the body with a short terminal half-life of 2.5h; it is mainly excreted in the urine via the kidneys [122]. Taking into account the pivotal role of the kidneys in the clearance of tianeptine, individuals with impaired kidney function exhibit altered tianeptine pharmacokinetic properties. Clinical studies on volunteers with varying degrees of renal impairment report an elongation in the terminal half-life of tianeptine [124]. Moreover, there seems to be a dramatic heightening of the terminal half-life of the metabolite MC5 in patients with renal failure [124].

In healthy elderly populations, the pharmacokinetic characteristics of tianeptine are very similar to those of healthy younger adults. A moderate increase of 1.0h is observed in the terminal half-life of tianeptine [125]. However, a major difference between these populations lies in the levels of the metabolite MC5, with significantly higher levels being observed in the elderly [125]. Since MC5 has a longer half-life than tianeptine and exhibits pharmacological activity, the occurrence of adverse effects may be higher in elderly and reduced doses may be appropriate.

Tianeptine has been associated with gender-specific differences in efficacy which may be attributable to gender differences in pharmacokinetics. In females the volume of distribution is modestly lower when compared to that of males; specifically, the volume of distribution is 31% lower in women [126]. While most clinicians believe that this difference is of no clinical significance, it may indeed explain the reason as to why some clinical studies have reported tianeptine to be more efficacious in male populations.

6. Conclusion

Clinically tianeptine is as efficacious as SSRIs with more rapid improvements in cognitive function and anxiety relieving properties. What is more, in terms of safety and tolerability tianeptine is particularly attractive since clinical studies have shown it to be less hazardous and significantly less prone to disrupting the patient's normal functionality. Tianeptine's multimodal pharmacology, summarized in figure 1, may underlie this clinical profile. Tianeptine is an atypical antidepressant acting at SERT to stimulate serotonin reuptake, although this mechanism is unlikely to explain tianeptine's antidepressant properties. One more plausible mechanism by which tianeptine produces its antidepressant and neurorestorative properties is via modulation of the glutamatergic system which is achieved by an effect upon the glycine site of the NMDA receptor; inhibiting its function, and mTOR signalling by indirectly enhancing AMPA-related signalling. Additionally, tianeptine's antidepressant actions in mice have recently been shown to be dependent on the μ-receptor which in turn could activate mTOR signalling to enhance AMPA related signalling. Tianeptine itself is off patent, but it still holds much promise as an experimental tool, yielding valuable insights into the molecular mechanisms underlying depression.

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Figure 1. Proposed pharmacological mechanisms of action of the multimodal antidepressant tianeptine. Tianeptine binds to the serotonin reuptake transporter (SERT) and may enhance synaptic levels of serotonin although this mechanism is unlikely to account for antidepressant effects. Tianeptine interacts with the glycine modulatory site of the glutamate ionotropic NMDA receptor which could alter mammalian/mechanistic target of rapamycin (mTOR) signalling and affect downstream mediators such as brain derived neurotrophic factor (BDNF) and the glutamate ionotropic AMPA receptor. Furthermore, tianeptine is an agonist at μ–opioid receptors (μOR) which could also activate mTOR signalling and stimulate dopamine release.
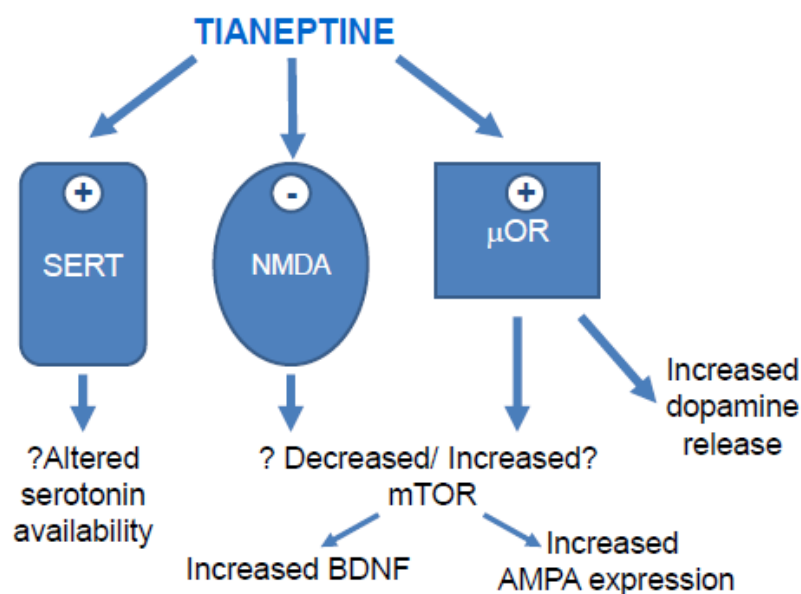
Table 1. Summary of clinical trials and case reports of patients with major depressive disorder (MDD) and bipolar disorder taking tianeptine. Reports are presented in chronological order and is an attempt to list all the available trials accessed via PubMed database search. The experimental study design, depression rating scales

used to determine outcomes, results and adverse effects/safety/tolerability are commented on.

REFERENCE	PATIENT PROFILE	EXPERIMENTAL DESIGN	OUTCOME MEASURES	RESULTS	ADVERSE-EFFECTS
Alby et al., 1993	206 patients, both genders, with MDD and dysthymia with associated somatic complaints	90-day double-blind trial comparing the efficacy and acceptability of tianeptine (37.5 mg/day) versus fluoxetine	HARD and FARD scores	Tianeptine and fluoxetine produced identical efficacy in terms of antidepressant and anxiolytic response as well as improvement in somatic complaints. Fluoxetine treated patients however required tranquilizers more often added to their prescription in order to achieve similar antidepressant response as patients taking tianeptine	Tianeptine was well tolerated by patients
Invernizzi et al., 1994	300 MDD patients, both genders	6 week double-blind controlled study comparing tianeptine (37.5 mg/day) to amitriptyline	HDRS, SAD, CGI Scores	Tianeptine is an effective antidepressant and is associated with less somatic complaints and side effects when compared to amytriptiline	
Ansseau et al., 1996	152 patients with adjustment disorder with mixed emotional features (anxiety and depression), both genders	6 week multicenter comparison study of tianeptine(37.5 mg/day) versus alprazolam and mianserin	CGI,HARS, MADRS, VAS, AMPD Scores	Tianeptine produces equipotent anxiolytic effects with alprazolam and mianserin	Tianeptine was associated with clinically insignificant side-effects
Cassano et al., 1996	187 MDD and Bipolar Disorder patients, both genders	6 Week Double-blind parallel group study of tianeptine (25-50 mg/day; mean dose 37.5 mg/day) versus placebo and imipramine.	MADRS Scores	Tianeptine is effective in the treatment of MDD and depression associated with bipolar disorder. No difference in efficacy was found between tianeptine and imipramine	No difference in adverse effects was found between tianeptine and placebo. Assessment of hematological ,renal, metabolic and hepatic parameters confirmed safety of tianeptine; it produces no side-effects associated with the tricyclic antidepressant imipramine
Costa e Silva et	126 MDD and	42 days long	MADRS,	Tianeptine is effective in the	Tianeptine's acceptability did not

al., 1997	Bipolar Disorder patients, Depressed with or without melancholia, both genders	multicentre randomised, double-blind, parallel group study of tianeptine (25-50 mg/day; mean dose 37.5 mg/day) versus placebo	CGI, HARS, Zung DSR and VAS scores	treatment for patients with MDD or Bipolar Disorder associated Depression, with or without melancholic features	differ from that of placebo. For adverse events, a higher incidence of headaches was found with tianeptine.
Vandel et al., 1999	30 year old female MDD patient	Case study reporting the abuse potential of tianeptine (37.5 mg/day)	Abuse potential was assessed based on whether the patients altered the dosage regime on their own	Tianeptine was associated with abuse potential with the patient spontaneously increasing the dosage which after two months reached 150 tablets per day. The discontinuation of the tianeptine treatment occurred four days after hospitalization.	150mg/day of tianeptine was not associated with any severe toxic effects. In the beginning of this high treatment period reported nausea, vomiting, abdominal pain, anorexia with weight loss, constipation; these side effects progressively disappeared.
Delery et al., 2001	268 recurrent MDD patients, both genders	6-week multicentre open cooperative study of tianeptine (37.5 mg/day) versus placebo	Kaplan-Meier survival curve analysis	Tianeptine decreases relapse and recurrence of MDD by two to threefold compared to placebo and was supported for use in the long-term treatment of MDD	No difference in adverse effects was found between tianeptine and placebo.
Guelfi et al., 2001	1858 MDD without melancholia or psychotic features patients, both genders	3-month long open study in general practice assessing tianeptine (37.5 mg/day) acceptability	MADRS Scores	Tianeptine was not associated with cardiovascular, hematologic, hepatic and biochemical abnormalities while it was not associated with dependence nor with withdrawal symptoms following discontinuation of treatment	
Lepine et al., 2001	366 MDD patients without past or current history of co-morbid anxiety and/or important anxiolytic treatment, both genders	6-week, double blind comparison trial of tianeptine (37.5 mg/day) with paroxetine effectiveness with special focus on improvement anxious symptoms	MADRS and HDRS Scores	Tianeptine and paroxetine exhibited equipotent efficacy on depressive symptomatology and act directly on the anxious components of depression	Tolerability of both drugs was good, although significantly better with tianeptine

Kasper and Olie, 2002	1378 MDD patients, both genders	Meta-analysis comparing the efficacy of tianeptine (37.5 mg/day) versus fluoxetine in the short treatment of depression	MADRS AND CGI Scores	Both tianeptine and fluoxetine produced significant antidepressant response with greater efficacy in favor of tianeptine	Tianeptine has a better acceptability profile than the SSRI fluoxetine
Novotny and Faltus, 2002	178 MDD patients, both genders	6-week, multicentre, randomised, double-blind controlled study comparing tianeptine (37.5 mg/day) to fluoxetine	MADRS, CGI, COVI Scores	Tianeptine was as efficacious as fluoxetine in its antidepressant response and was well tolerated by patients	
Bonierbale et al., 2003	237 male patients with mild to moderate depression with erectile dysfunction	8-weeks randomized, double-blind, placebo-controlled, crossover trial of tianeptine (37.5 mg/day)	ADS, Brief Sexual Inventory, and Quality-of-life and erection questionnaire scores	Tianeptine significantly improved the males erection when controlled with males on placebo	
Guillem and Lepin, 2003	42 year old male MDD patient	Case study reporting the abuse potential of tianeptine (37.5 mg/day)		The patient alleged a "flash sensation" like with heroin with the very first doses, psychological well-being sensation, better psychomotor performances and transient mood elation. His addiction to tianeptine was immediate and heavy, reaching 240 tablets/day. The positive reinforcement faded away after one month and a total dependence took over, with physical and psychological withdrawal symptoms when doses were not renewed.	
Letere et al., 2003	5 MDD patients, both genders	Case study reporting five cases of excessive consumption of tianeptine (37.5 mg/day)	DSM IV, CIM 10 criteria	The five patients exhibited pathological profiles of psychoactive drug abusers in that tianeptine was always used in higher than recommended dosages and was taken in association with other psychotropes.	Withdrawal due to tianeptine misuse was difficult and induced anxiety and other disorders and led to relapse in most of the patients

Nickel et al., 2003	42 MDD and Bipolar Disorder patients, both genders	42 days double-blind randomized controlled studies comparing the clinical and neurobiological effects of tianeptine (37.5 mg/day) versus paroxetine	HAMD, MADRS, CGI, BDI	Tianeptine and paroxetine improved depressive symptomatology, restored neurobiology and enhanced cognition equipotently. Paroxetine, however was associated with a better response amongst women	Tianeptine was well tolerated by patients
Niederhofer, 2003	32 year old female patient with treatment resistant MDD	Case study reporting the effectiveness of tianeptine (≤37.5mg/day) as a add-on therapy in treatment resistant depression	HAM-D	Combination of antidepressants and Tianeptine significantly reduced depression symptomatology in treatment resistant depression	Combination of tianeptine with other classes of antidepressants was well tolerated
Murck et al., 2003	38 MDD patients, both genders	42-day comparative trial assessing the effects of tianeptine (37.5mg/day) versus paroxetine on sleep regulation	Spectral analysis of the non-REM sleep EEG	Spectral analysis of the non-REM sleep EEG revealed a strong decline in the higher sigma frequency range (14-16 Hz) in male treatment responders independent of medication. The patients receiving paroxetine showed less REM sleep and more intermittent wakefulness compared to the patients receiving tianeptine	Tianpetine was well tolerated by patients
Saatcioglu et al., 2006	24 year old MDD patient	Case study reporting the abuse potential of tianpetine (37.5mg/day)	Abuse potential of tianpetine assessed based on symptoms and spontaneous increases in dosage regimes	Tianeptine was associated a strong feeling of wellbeing when taken and led to physical withdrawal symptoms following abrupt discontinuation. Moreover it led to tolerance and the patient had to increase the dosage to experience tianeptine's positive reinforcing properties; specifically the patient was reported to reach doses as high as 3000mg/day.	3000mg/day of tianeptine was excellently tolerated by the patient and did not alter hepatic parameters.
Kisa et al., 2007	34 year old	Case study	Abuse	Tianpetine was associated with psychostimuant effects that led to	

	female MDD patient	reporting the abuse potential of tianeptine (37.5mg/day)	potential of tianeptine was assessed based on symptomatology and spontaneous increases in dosage regimes	misuse (with the patient reaching doses of 750mg/day) and dependence. Moreover tianeptine led to symptoms of deprivation in the absence of the drug.	
Ari et al., 2010	33 year old female MDD patient	Case study assessing the potential use of naloxone in tianeptine overdose	Improvement in the Glasgow coma score	Naloxone combination with supportive care is an effective treatment regime for the management of tianeptine poisoning. Exact dosages that lead to tianeptine toxicity were not reported	
Woo et al., 2013	150 MDD patients that had not responded to previous SSRI monotherapy, both genders	6-week open-label study comparing the efficacy of tianeptine (≤37.5mg/day) as an add-on therapy	HDRS,MADRS and CGI Scores	A combination strategy with tianeptine may be an effective and well-tolerated tool for patients who have failed to adequately respond to SSRI monotherapy.	Tianeptine and SSRI combination was generally well-tolerated.
Jeon et al., 2014	164 MDD patients, both genders	12-week, multicentre, randomized comparative trial of tianeptine (37.5mg/day) versus escitalopram on improvement of neurocognitive function	Mini-Mental State Examination, the Continuous Performance Test(MMSE), the Verbal Learning Test(VLT), and the Raven Progressive Matrices(RPM)	Both drugs improved subjective cognitive impairment of memory and concentration. Tianeptine, however, led to more profound improvements in neurocognitive functions, especially in commission errors and verbal immediate memory, compared with escitalopram,	Tianeptine was well tolerated by patients
Yoo et al., 2015	164 MDD	12-week,	HAM-A,	Improvement in anxiety symptoms	Tianeptine was well tolerated by

	patients, both genders	multicentre, randomized trial comparing tianeptine (37.5mg/day) to escitalopram	HAM-D, MMSE,CPT, VLT,RPM	due to tianeptine and escitalopram use were significantly associated with improvement in subjective and objective neurocognitive functions such as delayed memory and reasoning ability in elderly MDD patients; However it was not associated with improvements on immediate memory and commission error	patients
Bence et al., 2016	Pregnant female MDD patient	Case study reporting the impact of tianeptine (37.5mg/day) abuse on the mother-child dyad	Abuse potential assessed based on symptom and spontaneous increases in tianeptine doses	The female patient presented with dependence on tianeptine, with the use of >650 mg of the drug per day. The state of dependence remained unidentified throughout the first pregnancy, but just after delivery, her full-term newborn exhibited unexpected neonatal abstinence syndrome (NAS) which was successfully treated with morphine.	