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Neurobiological and Clinical Effects of the Antidepressant Tianeptine

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Abstract

The precise neurobiological processes involved in depression are not clear, but it is recognized that numerous factors are involved, including changes in neurotransmitter systems and brain plasticity. Neuroplasticity refers to the ability of the brain to adapt functionally and structurally to stimuli. Impairment of neuroplasticity in the hippocampus, amygdala and cortex is hypothesized to be the mechanism by which cognitive function, learning, memory and emotions are altered in depression. The mechanisms underlying alterations in neuroplasticity are believed to relate to changes in neurotransmitters, hormones and growth factors. Structural changes in the hippocampus that have been proposed to be associated with depression include dendritic atrophy, reduced levels of cerebral metabolites, decreased adult neurogenesis (generation of new nerve cells) and reduced volume. Increased dendritic branching occurs in the basolateral nucleus of the amygdala. Reduced neuronal size and glial cell density occur in the prefrontal cortex.

Clinically, tianeptine is an antidepressant effective in reducing symptoms of depression in mild to moderate-to-severe major depression, including over the long term. Tianeptine is also effective in alleviating the symptoms of depression-associated anxiety. It is generally well tolerated, with little sedation or cognitive impairment.

The efficacy profile of tianeptine could be explained by its neurobiological properties observed in animal models. Tianeptine prevents or reverses stress-associated structural and cellular changes in the brain and normalizes disrupted glutamatergic neurotransmission. In particular, in the hippocampus, it prevents stress-induced dendritic atrophy, improves neurogenesis, reduces apoptosis and

normalizes metabolite levels and hippocampal volume. Tianeptine also has beneficial effects in the amygdala and cortex and can reverse the effects of stress on neuronal and synaptic functioning.

The neurobiological properties of tianeptine may provide an explanation not only for its antidepressant activity, but also for its anxiolytic effects in depressed patients and its lack of adverse effects on cognitive function and memory.

Depression is one of the most common mental disorders. There are numerous theories for the aetiology of this disorder, including psychological, social, endocrine, biochemical and genetic causes.[1] Several factors may make a person more vulnerable to a first episode or a recurrent episode of depression; personality factors, a family history of depressive illness, childhood experiences and stressful life events.[1] Although about one-half of patients will experience only one episode of depression, for those with recurring episodes, the risk of a recurrent episode is greatly increased by the number of prior episodes.[1] Depression can therefore be a debilitating disease and have significant impact on the quality of life of the patient.[1]

Given that there is a wide range of causes, presentation, clinical course and prognosis of this disorder,[1] it is not surprising that the biological basis of depression is complex and the precise neurobiological processes involved are not clear. The predominant theory has been that the primary aetiological factor could be an imbalance in neurotransmission by monoamines (the 'monoamine hypothesis' of depression), particularly serotonin and noradrenaline (norepinephrine), leading to deficient levels of these neurotransmitters.[2] This hypothesis is supported by the fact that many antidepressants block the reuptake or enzymatic oxidation of monoamines.[3] As a result, much research in depression for the past 20 years has focussed on the synapse and neurotransmitters.

Recently, the role of altered or impaired neuroplasticity – defined as the ability of the brain to adapt functionally and structurally to stimuli[4,5] – in the pathogenesis of depression has been investigated in both animal and human studies (table I). Neuroplasticity should not be confused with neurogenesis, which is the generation of new nerve cells.[6] Various factors including the psychological environment, traumatic events, genetic traits and

Table I. Alterations in neuroplasticity in depression

Animal models of depression
Dendritic remodelling in hippocampal CA3 pyramidal neurons, with reversible shortening and debranching of apical dendrites (atrophy). Mechanism involves high levels of glucocorticoid secretion[7,8]
Reduction in hippocampal volume, decreased level of the cerebral metabolite *N*-acetyl-aspartate (a marker of neuronal viability), and decreased proliferation rate of granule precursor cells in the dentate gyrus[2,9,10]
Decreased adult neurogenesis in the dentate gyrus[9,11]
Increased dendritic arborization in the spiny pyramidal and stellate neurons of the basolateral amygdala[2,9,12]
Patients with chronic depression
Reduced volume of grey and white matter in prefrontal cortex[13,14]
Reduced hippocampal volume (by ≈10–20%).[15-17] Atrophy occurs after repeated depressive episodes but is generally not evident in a first episode[18]
In patients with chronic depression, no change in total amygdala volume but core nuclei amygdala volume reduced,[19] whereas in patients with first episode depression, total amygdala volume is increased[20]
Reduced medial orbitofrontal (gyrus rectus) cortical volume[13]
Changes in blood flow and glucose metabolism in the hippocampus and amygdala[9]
Reduced brain activity (brain oxygenation) in the prefrontal cortex[21]
Reduced neuronal size and/or decreased density of glial cells in areas of the prefrontal cortex[22-24] and the amygdala[25]

somatic disease are known to influence the occurrence of depression,[1] which may lead to morphological and functional changes in the brain.[5] For example, disrupted or abnormal neuroplasticity due to inappropriate or prolonged stress can lead to an inability of the brain to make the appropriate responses to stimuli.[5]

Neurotransmitter and neuroendocrine pathways that may mediate adaptive responses to stress include the hypothalamic-pituitary-adrenal (HPA) axis,[9] the glutamatergic system,[9] and growth hormones[4] such as brain-derived neurotrophic factor (BDNF).[26]

Regions of the brain where impaired plasticity and concomitant structural changes are associated with depression are the hippocampus, amygdala and prefrontal cortex.[26] In animals[27] and humans,[13,15-18,20,22,23,25,28-30] changes in these areas can encompass reductions in volume,[13,15,17,25,29] neuronal size and density,[18,22] neurogenesis[27] and glial density,[16,18,22,23] increased amygdala volume,[20] and changes in cerebral blood flow and glucose metabolism[28,30] (table I). It is thought that alterations in these brain regions affect emotions, mood, memory and cognitive function, thus possibly producing the symptoms characteristic of depression.[26]

The changes in neuroplasticity are potentially reversible, even in patients with established atrophy, and, therefore, the mechanisms underlying changes in neuroplasticity provide a target for antidepressant therapy.[27] The correction of stress-induced changes in neuroplasticity reflects a new direction for antidepressant therapy.[31,32]

The antidepressant tianeptine has shown some potentially beneficial neurobiological properties, including effects on neuroplasticity and various neurotransmitter systems, such as the glutamatergic system.[2] Tianeptine differs from other antidepressants in its pharmacological and neurochemical properties (see table II for a summary of the pharmacological properties of tianeptine).[33-35] The established antidepressant efficacy of tianeptine, proven in placebo- and comparator-controlled studies and a meta-analysis (see section 2.1), cannot be explained in terms of the monoamine hypothesis, illustrating the limitations in our understanding of mood disorders and depression. The fact that electroconvulsive therapy (ECT) is also clearly established as a treatment for depression,[36] confirms that, although long-standing, the monoamine hypothesis of the pathophysiology of depression is at least incomplete. In addition, the monoamine hypothesis cannot account for the delay in onset of action of typical antidepressants of several weeks, why antidepressants are also effective in other mental disorders such as panic disorder and obsessive-compulsive disorder, why not all drugs that increase monoamine transmitter levels in the brain are effective antidepressants,[3] or why agents such as tianeptine that do not increase monoamine transmitter levels are effective antidepressants.[36]

This article reviews the mechanism of action of tianeptine, its neurobiological properties and preclinical and clinical data in the context of the neurobiology of depression, in an attempt to provide a possible explanation for the observed beneficial clinical profile of tianeptine in patients with major depression.

1. Tianeptine and the Neurobiology of Depression

The neurobiology of depression is complex. Studies that attempt to elucidate the underlying pathobiology of depression and the mechanism of action of antidepressants tend to focus on specific neurotransmitter systems and specific areas of the brain, and may use animal models of depression.

1.1 Brain Structure and Neuroplasticity

The hypothesis that alternations in neuroplasticity are implicated in the pathophysiology of depression is supported by a body of evidence from neuroimaging and postmortem studies in patients with depression and from animal models of depression that show modifications in key regions of the brain (table I).

Recent neurobiological evidence in human subjects suggests that mood disorders, such as major depressive disorder, are characterized by neuron

Table II. General pharmacological properties of tianeptine (reproduced from Wagstaff et al.,[33] with permission)

Animal models
Increases uptake of serotonin in the cortex and hippocampus. Despite no direct effect on reuptake of noradrenaline (norepinephrine) or dopamine, levels of these neurotransmitters are indirectly increased in several brain regions
Activity selective for serotonergic mechanisms, and essentially presynaptic. Has no, or low, affinity for neurotransmitter receptors
Antidepressant activity shown in classical screening tests and models of depression
Activity appears to be dependent on the (−) enantiomer. The predominant metabolite (MC5, pentanoic acid) has some antidepressant activity, but significantly less than the parent compound
Anxiolytic activity in some (but not all) models. Not associated with sedative effects
Antinociceptive/analgesic activity
Improves both working and reference memory
Decreases ethanol intake and alleviates effects of ethanol and ethanol withdrawal
Healthy volunteers and patients
Cognitive function (attention, memory, reasoning) not adversely affected in healthy volunteers; indications of improvement in memory and attention
No measurable effects on psychomotor performance or driving skills vs placebo in healthy volunteers
Slight activating properties (EEG), mood elevation and improved attention in healthy volunteers, vs initial sedation with fluvoxamine
No effects on objective sleep parameters in healthy volunteers
Antidepressant and anxiolytic effects, without sedation or adverse effects on sleep, and with positive effects on impaired memory in patients with alcoholism and concurrent depression after alcohol withdrawal
No effects on cardiovascular parameters (blood pressure, ECG, heart rate, echocardiography, ventriculography) in young healthy volunteers
Indications of efficacy in patients with panic disorder substantiated by EEG data
Blunted prolactin response to dexfenfluramine in healthy volunteers

atrophy, cell loss and/or impairments in neuroplasticity and cellular resilience.[37] The hippocampus has been implicated in the pathophysiology of depression. It is one of the main sites of adult neurogenesis in animals[6] and is the region of the brain that controls learning, cognition, anxiety and the HPA axis.[26] It has been suggested that structural damage to this region of the brain is associated with deficits in these functions, which may lead to the cognitive and anxiety symptoms of depression. A study by van der Flier et al.[38] found that memory complaints and depressive symptoms were associated with reduced left hippocampal volume in otherwise healthy volunteers with memory complaints and no cognitive impairment. In a small study of 14 patients with depression, the severity of subjective memory impairment correlated with decreasing right hippocampal volume.[39] In a study comparing hippocampal volume in 16 patients with major depression and 16 case-matched nondepressed control subjects, depressed patients had a 19% smaller left hippocampal volume than control subjects ($p < 0.05$), without smaller volumes of comparison brain regions or whole brain volume.[15] Similarly, Duman and Monteggia[26] have postulated that the changes in the prefrontal cortex (responsible for working memory, cognition and mood) and the amygdala (responsible for emotional control and anxiety) [table I] might be able to explain the cognitive and/or behavioural symptoms seen in patients with depression. For example, chronic stress-induced amygdala dendritic remodelling was associated with increased anxiety-like behaviour in a rat model of depression.[40] Whether the structural changes are directly responsible for the development of depression could be open to debate.[6]

Stress paradigms have been used as animal models for depression to investigate the short-term actions of antidepressants on brain structure and neuroplasticity. In such models, tianeptine opposed the effects of chronic stress on brain structure and plasticity. For example, tianeptine prevented structural changes and modified neuronal metabolism and function in the hippocampus in tree shrews subjected to psychosocial stress.[10] In this study, 'chronic' (28 days) treatment with tianeptine re-

versed the acute stress-induced decreases in hippocampal volume, levels of cerebral metabolites such as *N*-acetyl-aspartate, and proliferation of the granule precursor cells in the dentate gyrus.[10]

In animal studies, tianeptine has also been shown to prevent and reverse stress-induced glucocorticoid-mediated dendritic atrophy in CA3 pyramidal neurons in the hippocampus[27,41] and stress-induced increases in dendritic length and branching in the amygdala.[7] These studies were performed in rats and atrophy was assessed by measuring the length and number of apical dendrite branch points. Only one study[27] investigated the effect of other antidepressants; the serotonin reuptake inhibitors fluoxetine and fluvoxamine failed to block dendritic atrophy.

In addition to normalizing the rate of cytogenesis in the hippocampus,[10] chronic tianeptine treatment reduced apoptosis in the dentate gyrus of the hippocampus and the temporal cortex in psychosocially stressed tree shrews.[42] It also appeared to be cytoprotective against the effects of proinflammatory cytokines in the cortex and white matter in mice.[43] Data also suggest that tianeptine may promote neuroplasticity by increasing expression of genes of neuroplastic factors that are decreased in animal models of stress. These include the genes for BDNF[44,45] and nerve growth factor[44] in the hippocampus[44] and amygdala.[45]

Studies of the role of intracellular signal transduction and regulation of gene expression in impaired neuroplasticity in depression has led to the 'neurotrophic hypothesis of depression' (reviewed in detail elsewhere by Duman and Monteggia[26]) with BDNF an important mediator of neuronal plasticity and a potential target for antidepressant drug development.[5] Briefly, this hypothesis is based on the observation that stress has been shown to decrease BDNF expression in the hippocampus, which may contribute to the neuronal atrophy and neuronal cell loss in key limbic regions in the brain seen in patients with depression;[26] conversely, chronic antidepressant treatment, including with SSRIs, MAOIs, SNRIs, atypical antidepressants and electroconvulsive seizures, increased hippocampal expression of this neurotrophic factor.[26] Although there is a growing body of evidence supporting this hypothesis, which links brain structure, neuroplasticity, neurogenesis and the pathobiology of depression, further research is required. Other hypotheses for the neurobiology of depression have been proposed,[36] but are beyond the scope of this review.

1.2 Synaptic Function

Synaptic function has a role in the pathophysiology of depression. Studies have shown that stress can affect synaptic function. For example, stress has been shown to impair hippocampal synaptic function and enhance amygdala processing in animals.[46] Tianeptine enhanced synaptic plasticity in the hippocampus and prefrontal cortex without adversely affecting amygdala synaptic function in animal models of stress.[12,46-48] For example, in rats, acute administration of tianeptine reversed the inhibitory effect of acute stress on long-term potentiation (enhanced synaptic transmission) in the prefrontal cortex[47] and hippocampal CA1 area,[48] and blocked the inhibitory effects of acute stress on primed burst potentiation in hippocampal CA1, without altering stress-enhanced long-term potentiation in the basolateral nucleus of the amygdala.[12] These data suggest that tianeptine should enhance hippocampal and prefrontal cortex memory-related processing in people under stress.[46]

Acute tianeptine prevented the impairment in long-term potentiation induced by acute stress for the first 2 hours post long-term potentiation induction; fluoxetine produced a similar effect but only for 1 hour post long-term potentiation induction.[47] Indeed, coadministration of tianeptine and fluoxetine inhibited the effect of tianeptine on reversal of the effect of stress on long-term potentiation in the hippocampal CA1 area.[48] The latter findings are consistent with the opposite effects of tianeptine and fluoxetine on serotonin reuptake.[48]

1.3 Glutamatergic System

Synaptic transmission depends on careful regulation of neurotransmitters. One of the excitatory amino acids, glutamate, is a key cerebral excitatory

neurotransmitter.[49,50] It is involved in nearly all aspects of brain function and is implicated in the pathophysiology of depression.[51] The release of glutamate is regulated by glucocorticoid hormones secreted in response to stress activation of the HPA axis.[50] The role of glutamate and glutamatergic receptors in mood disorders has been previously reviewed.[52] Briefly, animal studies have demonstrated that in stress conditions, extracellular glutamate levels are modestly increased in the hippocampus[53,54] and in the amygdala;[55] and these abnormal levels can lead to reductions in neuronal size and density and hippocampal volume.[53] In contrast, high levels of glutamate in the synaptic space are neurotoxic, causing excessive activation of glutamate neuronal receptors in a process referred to as 'excitotoxicity'.[56] Evidence that glutamate is involved in the regulation of neuroplasticity comes from animal studies where blockade of the glutamate NMDA receptor, with an antagonist,[27,57] prevents deleterious effects of stress, whereas activation of NMDA receptors decreased neurogenesis.[11] Thus, regulation of glutamatergic transmission could be an important component of neuroplasticity.[9] Indeed, altered neuroplasticity via disturbed glutamatergic neurotransmission has been shown to result in the type of neuronal dysfunction associated with depression.[52] In patients with major depression, functional imaging studies have suggested a possible role of altered glutamatergic neurotransmission within the anterior cingulate in the pathogenesis of mood disorders.[58] Normalizing the glutamatergic system is therefore a potential treatment target in patients with depression.

Tianeptine has been shown to inhibit the pathological stress-induced changes in glutamatergic neurotransmission in the hippocampus and amygdala in animal models,[55,59] and the drug appears to normalize disrupted glutamatergic neurotransmission.[59,60] Further research is needed to determine the long-term effects of tianeptine. In the rat amygdala, acute administration of tianeptine, but not fluoxetine, inhibited acute stress-induced increases in glutamate efflux in the basolateral nucleus.[55] Tianeptine may also modulate the stress-induced changes observed in the expression of glutamate receptors;[60,61] chronic use of tianeptine increased phosphorylation of the CamKII/PKC site (Ser831) on the GluR1 subunit of glutamate AMPA receptors in the frontal cortex.[60] Preliminary reports of these preclinical studies indicate that chronic use of fluoxetine had a similar effect on phosphorylation, but at a different site of the GluR1 subunit (at Ser 845).[60] Also, tianeptine inhibited stress-related increases in glial glutamate transporter GLT-1 mRNA expression in the dentate gyrus and CA3 region of the rat hippocampus in the chronic restraint stress model of depression.[61] It also inhibited increases in GLT-1 protein levels in the CA3 region, but did not affect increased protein levels of the isoform GLT-1b.[61]

Further evidence for the mechanism of action of tianeptine in improving the symptoms of depression comes from animal models that show its effect on glutamate-activated signal transduction pathways. Tianeptine appeared to facilitate signal transduction at the CA3 commissural associational synapse by altering the phosphorylation state of glutamate receptors in an electrophysiological study in rats.[59] Chronic administration of tianeptine inhibited stress-induced re-scaling of the ratio of NMDA receptor- to AMPA/kainate receptor-mediated excitatory postsynaptic currents.[59]

1.4 Memory and Cognition

Glutamate receptors appear to be important in spatial learning, long-term potentiation, stimulus-response learning and memory, working memory, recognition memory and higher cognitive functions (reviewed by Robbins and Murphy[62]). Tianeptine has been shown to have beneficial short-term effects on cognitive function and memory function in animal models.[63-65] For example, tianeptine improved spontaneous alternation behaviour and spatial discrimination in normal mice, and improved sequential-specific alternation deficits induced by chronic alcohol intake in mice.[63] It has also been shown to prevent stress-induced impairment of spatial memory in rats.[64,65] A direct relationship between the effect of tianeptine on glutamate receptors

(see section 1.3) and its effect on cognitive function and memory has yet to be established.

Stress can lead to impaired memory function because the hippocampus, which is required for learning and memory, is susceptible to stress and hormone-related damage. This brain region is also involved in the negative feedback on the HPA axis stress response.[9] Campbell et al.[65] were able to demonstrate that the protective effect of tianeptine on memory in animals was not mediated by corticosterone (i.e. via the HPA axis) and they hypothesized that tianeptine may enable information to be stored in the hippocampus in such a way that it is protected from being impaired by later stress stimuli, possibly by normalizing stress-induced changes in the glutamatergic system.[65]

The effect of chronic stress on the amygdala is different to that on the hippocampus; in an animal model, stress caused damage to the hippocampus, but enhanced the function of the amygdala,[12] which is a region of the brain proposed to be responsible for the acquisition and storage of emotional memory.[12] Although acute administration of tianeptine did not alter stress-induced enhancement of amygdala function in this study,[12] in another animal study, long-term tianeptine administration had an effect on fear circuitry in the amygdala.[66] In the latter study,[66] which compared the effect of tianeptine and the SSRI citalopram in auditory fear conditioning in rats, long-term administration of either agent reduced auditory fear conditioning (a model of emotional learning), whereas the effect of short-term administration was different; short-term citalopram exacerbated the anxiogenic effect but tianeptine did not. The investigators concluded that these data are consistent with the clinical effects of SSRI treatment of anxiety disorders, in which a transient increase in anxiety is seen during early stages of treatment, which decreases after several weeks of treatment.[66]

2. Clinical Efficacy and Tolerability of Tianeptine

Tianeptine is effective in the treatment of patients with depressive disorders, including those with concomitant depression and anxiety. The clinical efficacy of tianeptine has been reviewed in depth by Wagstaff et al.[33] Two studies reported as abstracts at the time of that review have since been published as full papers[67,68] and an additional trial has been reported.[69] Tianeptine has been evaluated in double-blind, comparative trials in patients with major depression (unipolar depression), bipolar depression, dysthymia and adjustment disorder.

2.1 Antidepressant and Anxiolytic Efficacy

Tianeptine is an antidepressant with proven efficacy in reducing the symptoms of depression. The antidepressant efficacy of tianeptine has been established in two short-term, placebo-controlled trials, with tianeptine achieving statistically and clinically significant reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) scores compared with placebo ($p < 0.05$) [figure 1].[70,71] In a long-term extension study,[72] 185 tianeptine responders

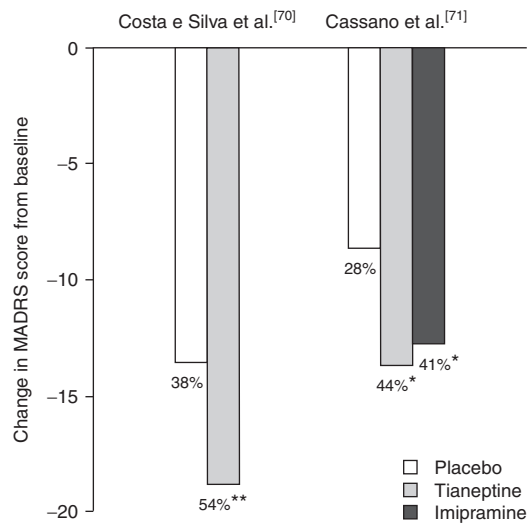

Fig. 1. Efficacy of tianeptine in double-blind, placebo-controlled trials in patients with depression. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline in patients with major depression or bipolar disorder receiving tianeptine 25–50 mg/day, imipramine 100–200 mg/day or placebo for 6 weeks. Data were analysed using the intention-to-treat populations (n = 123[70] and 186[71]). Percentage reduction from baseline given under each bar (greater reductions are associated with greater efficacy) [reproduced from Wagstaff et al.,[33] with permission]. * $p < 0.05$, ** $p < 0.01$ vs placebo.

from a 6-week, multicentre open-label study of inpatients with major depression were randomized to tianeptine 37.5 mg/day (n = 111) or placebo (n = 74) for up to 18 months (mean 16.5 months). Relapse (before 6 months) and recurrence (after 6 months), defined by a Hamilton Depression Rating Scale score of ≥15 and/or a Clinical Global Impression scale score of ≥4, were significantly less frequent in patients receiving tianeptine than in those receiving placebo ($p = 0.002$), and a higher proportion of tianeptine-treated patients had no relapse or recurrence ($p < 0.001$ vs placebo).

In comparisons with other antidepressants, tianeptine was generally equivalent to amitriptyline (n = 107–284),[73-75] imipramine (n = 186),[76] mianserin (n = 152 and 299),[77,78] paroxetine (n = 327)[69] and fluoxetine (n = 178–381)[79-82] in double-blind studies of 4–24 weeks' duration. A meta-analysis of studies comparing tianeptine to SSRIs (two studies comparing tianeptine versus fluoxetine, two studies comparing tianeptine versus paroxetine and one study comparing tianeptine versus sertraline [n = 1348]) confirmed that the efficacy of tianeptine after 6 weeks' treatment is statistically equivalent to that of SSRIs.[83] In these trials, tianeptine 25–50 mg/day generally achieved reductions from baseline in MADRS scores of around 50–60%.

There is evidence suggesting an anxiolytic effect for tianeptine, in patients with concomitant depression. In clinical trials, tianeptine was demonstrated to be similar to amitriptyline,[73-75] mianserin,[77,78] fluoxetine[79] and paroxetine[69] at improving anxiety symptoms in depressed patients in studies of between 4 and 24 weeks' duration. Tianeptine generally reduced Hamilton Anxiety Rating Scale (HAM-A) scores from baseline by approximately 50–60%. Antidepressant and anxiolytic efficacy with 4 weeks' tianeptine treatment is also seen in 107 patients with depression or dysthymic disorder associated with chronic alcoholism.[75] A 6-week, randomized, double-blind study compared the efficacy of tianeptine with the antidepressant mianserin 60 mg/day and the anxiolytic alprazolam 1.5 mg/day in 152 patients with adjustment disorder with mixed anxiety and depression. Similar efficacy was seen in all three treatment groups on all rating instruments,[77] although the possibility that this study simply detected a placebo effect cannot be eliminated as a placebo arm was not included. In a 90-day double-blind study comparing tianeptine and fluoxetine therapy in 206 patients with major depression or dysthymia, tianeptine recipients required significantly less concomitant anxiolytic treatment than those receiving fluoxetine at day 30, 60 and 90 ($p < 0.05$).[79] Anxiolytic therapy was reduced by 50% over 90 days in the tianeptine group versus no change in the fluoxetine group.[79]

2.2 Tolerability

Tianeptine is generally well tolerated. As reviewed by Wagstaff et al.,[33] the most common adverse events reported in clinical trials in depressed patients were gastrointestinal (nausea, constipation, abdominal pain) or related to the CNS (headache, dizziness and changes in dreaming). It is associated with a lower sedative effect and fewer adverse effects on attention and memory than TCAs, has a favourable cardiovascular profile, and is not associated with weight gain.[33] In this respect, the tolerability profile is generally similar to that observed with SSRIs.[33] However, in a subsequently published 6-week, double-blind trial in patients with major depression without any co-morbid anxiety disorder, the tolerability of both tianeptine and paroxetine was good, although significantly better with tianeptine ($p = 0.026$).[69] The most frequently reported adverse events were nausea (7%) and headache (6%) in the tianeptine group and nausea (15%), headache (8%), insomnia (6%) and dizziness (5%) with paroxetine.[69] Withdrawal rates were similar in the two groups, but significantly more patients in the paroxetine group discontinued as a result of adverse events (19 vs 6; $p < 0.05$).[69]

The prevalence of sexual dysfunction in patients with depression is very high. In a study performed in France,[84] a retrospective evaluation of sexual dysfunction in 4557 outpatients presenting with major depression, the prevalence of sexual dysfunction was 35% for spontaneously reported problems and 69% for problems identified by physician question-

naire. The frequency of sexual dysfunction was found to be higher in patients treated with antidepressants (TCAs, SSRIs and SNRIs) than in untreated patients (71% and 65%; $p < 0.01$). Analysis by treatment group showed that treatment with tianeptine was associated with a lower incidence of sexual dysfunction than treatment with TCAs or SSRIs; frequency was significantly higher with TCAs ($p < 0.005$) and SSRIs ($p < 0.001$) compared with untreated patients, whereas those treated with tianeptine had a similar rate of sexual dysfunction to untreated patients.[84]

Patients can experience discontinuation symptoms after cessation of antidepressant treatment, and this is true for most classes of antidepressants, although symptoms are not usually severe or long-term in nature.[85] We have been unable to find any reports of the occurrence of discontinuation symptoms with tianeptine. Discontinuation symptoms could lead to dependence, although this is rare with antidepressants. There is little evidence for the development of dependence in patients receiving tianeptine.[33]

Tianeptine has also been shown to be well tolerated in elderly patients. In a 1-year open-label, multicentre study of tianeptine treatment in 228 elderly patients, as few as 4.4% of patients withdrew because of adverse events (mainly drowsiness, anxiety or gastrointestinal disorders); the authors concluded that the benefit to risk ratio of tianeptine was very satisfactory, even in these elderly patients.[86]

3. Conclusions

It is now recognized that, in addition to the classical hypothesis of an imbalance of neurotransmission, factors such as stress, somatic disease and genetic predisposition can influence the occurrence of depression. These factors cause changes in a range of neurotransmitters, hormones and growth factors involved in the pathogenesis of depression. These changes are accompanied by structural changes in the brain (particularly in the hippocampus and amygdala). This is referred to as neuroplasticity, a term used to describe the ability of the brain to adapt functionally and structurally to stimuli (e.g. stress and other experiences). Although several lines of preclinical evidence support this hypothesis, many questions remain to be answered. As yet, there is no single accepted model of the pathobiology of depression.

The monoamine hypothesis of depression cannot explain the antidepressant efficacy of tianeptine. Tianeptine has multiple effects observed in animal studies that provide some insight into the drug's mechanism of action: (i) blockade of the mechanisms involved in functional changes to brain regions involved in depression; (ii) prevention and even reversal of depression-associated structural and cellular changes in the brain; and (iii) normalization of glutamatergic neurotransmission. We propose that the effects of tianeptine on glutamate may in part explain the mechanism of action of its antidepressant and anxiolytic efficacy observed in patients with depression, and its lack of adverse effects on cognitive function and memory.

Clinically, tianeptine is generally a well tolerated treatment and is effective in reducing symptoms of depression in mild to moderate-to-severe major depression.

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