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Less is More?
The Effect of Tianeptine and SSRI in the Treatment of Depression

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Abstract

Major depressive disorder (MDD) is rapidly growing among the population. A widely believed neurobiological explanation is that the symptoms arise due to an imbalance of the neurotransmitter serotonin. Therefore, the most provided antidepressant is currently selective serotonin reuptake inhibitors (SSRI), which increase the serotonin in the synaptic cleft by inhibit the reuptake of serotonin. There are medications which challenge the serotonin hypothesis such as tianeptine. Tianeptine increases the reuptake of serotonin in the synaptic cleft and thus decreasing the serotonin levels. The thesis has three aims: First, to investigate what mechanisms tianeptine and SSRI work upon. Second, compare the efficiency of SSRI and tianeptine. Third, if the two agents display any differences in adverse side effects. A systematic review and search through relevant databases were made to obtain results. The main findings of this thesis were the two agents act differently of many aspects of the brain mechanisms and neurochemistry such as the cannabinoid system, expression of different cell types and their dependence of protein kinase. Even so, the results show that both agents are equally efficient in treating the depressive symptoms in the larger context, although some interesting findings are seen when zooming in. Anxiety is often comorbid with depression and even though both tianeptine and SSRI are shown to reduce these symptoms during chronic administration, SSRI can produce an anxiogenic effect in the beginning. Another noteworthy finding was that tianeptine showed to be clinically significant, but so did placebo. The third aim investigated the differences in side-effects between these two agents, and both agents were equally safe in number of adverse side-effects. Though tianeptine showed to have some slight advantages in manners of sexual dysfunction and the item 3 on the CGI scale.

Keywords: Tianeptine, SSRI, Major depressive disorder, efficiency, side-effects, neurochemistry

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Introduction

We all feel negative affect in some situations and during some point in our life. It can be feelings of helplessness, sadness and emptiness, but for most of us, the emotion is brief and not very long-lasting. There is some sort of equilibrium of affect which sometimes brings us positive emotion and sometimes negative ones. A patient diagnosed with major depressive disorder the negative feelings are not as brief as in healthy individuals, instead, they are long-lasting persistent and affect their daily life (Gazzaniga, Heatherton, & Halpern, 2016; Kirsch et al., 2008). Their pattern of negative thoughts drains their energy and solely by the thought of an activity which used to bring them joy becomes stressful and the negative thoughts take over. This sometimes results in avoiding previously joyful activities. Accompanied by these negative feelings and thoughts are also symptoms such as sexual dysfunction, suicidal thoughts, thoughts about death, anhedonia and sleep disturbances to name a few (Gazzaniga et al., 2016).

According to the diagnostic and statistical manual of mental disorder, the fifth edition (DSM-5) there are certain criteria which need to be fulfilled to be diagnosed with MDD (Gazzaniga et al., 2016). The DSM-5 states that a person needs to have suffered an episode of major depression each day for a minimum of two weeks in which the following symptoms need to be present: 1. Experience moods of depression. 2. Anhedonia in forms of high decrease of interest and pleasure of activities (Gazzaniga et al., 2016). MDD is a growing issue and more than six percent of Americans are diagnosed every year, and the expectancy for an American to develop MDD during their life is believed to be 15 percent. Yet so, the disorder is most prominent in women of third world countries such as China, India and Pakistan and is the leading cause of suicide in these areas (Andrews, Thomson, Amstadter, & Neale, 2012; Gazzaniga et al., 2016).

There are different components in the development of depression such as situational, cognitive and biological (Gazzaniga et al., 2016). A widely believed neurobiological explanation of MDD is that the symptoms arise due to an imbalance of the neurotransmitter serotonin, but some researcher also suggests that a deficiency in neural plasticity also play a role (McEwen et al., 2010). Due to the serotonin hypothesis, a commonly used treatment to alleviate the symptoms of MDD are medications which increase the level of serotonin and monoamine. These kinds of medications are known as selective serotonin reuptake inhibitor (SSRI), since it blocks the reuptake of the neurotransmitter serotonin in the synaptic cleft (Nickel et al., 2003). Due to the reuptake inhibitor, more serotonin is available in the synaptic

cleft and can act on the post-synaptic receptors. Agents in which belongs to the SSRI class are citalopram, sertraline, fluoxetine, fluvoxamine, escitalopram and paroxetine.

The Challenge of Tianeptine

There are medications which challenge the serotonin hypothesis such as tianeptine. In contrary to SSRI, tianeptine triggers the reuptake of serotonin and thus decreasing the levels of serotonin in the synaptic cleft (Broqua, Baudrie, Laude, & Chaouloff, 1992; McEwen et al., 2010; Sacchetti, Bonini, CoolsWaeterloos, & Samanin, 1993). There is support for the uncertainty of whether SSRI is efficient and if it actually produces the desired effects of alleviating symptoms as expected (Andrews et al., 2012; Kirsch et al., 2008). Studies surface in which support the statement that SSRI is not as significantly eminent compared with placebo as it was first thought. Some studies have revealed that SSRI does not meet the criterion for clinical significance (Andrews et al., 2012; Kirsch et al., 2008). It does seem that the severity of the diagnosis is positively correlated with the relief of symptoms by SSRI. That is the more severe the diagnosis is, the better effect SSRI has on alleviating symptoms. Although it should be mentioned that this correlation is quite weak (Andrews et al., 2012; Kirsch et al., 2008). SSRI as an antidepressant also provides numerous unpleasant and unwanted side effects such as sexual dysfunction, attentional and memory deficits, and some studies claim they could do more harm than good in some cases (Andrews et al., 2012; Gazzaniga et al., 2016; McEwen et al., 2010).

SSRI becomes challenged by tianeptine since findings do not only show that tianeptine alleviate symptoms of depression but it also reduces the level of anxiety (Broqua et al., 1992; McEwen et al., 2010). Compared to other forms of antidepressants such as SSRI, tianeptine has shown to have a reduced number of side effects (McEwen et al., 2010). There is a glutamate release during stress which increases the glutamate levels in the hippocampus. These enhanced glutamate levels disturb the neurogenesis and thus the neuroplasticity in the hippocampus (McEwen et al., 2010). Tianeptine has shown to be effective in reducing these glutamate levels and thus restore the damage in neuroplasticity caused by stress (McEwen et al., 2010). The mechanisms of tianeptine are poorly known and research are trying to unravel this enigma. Despite the unfamiliar mechanisms of tianeptine it seems to produce desired effects and fewer side effects compared to SSRI and should, therefore, be examined more thoroughly.

Aim

As the literature on the matter speaks out, major depressive disorder is a growing issue in today's society and a large number of people will be affected by the disorder. The symptoms MDD produce are of great discomfort and even lethal in some cases and an efficient antidepressant which reduces symptoms are much needed. This thesis has three main aims. First, literature was reviewed to gain insight into what mechanisms tianeptine and SSRI work upon. Second, this thesis will also compare the efficiency of SSRI and tianeptine of reducing symptoms. Third, to investigate if there are any differences in adverse side effects of the tianeptine and SSRI.

To do so, a systematic review will be conducted where relevant articles and literature will be examined and evaluated.

Method

The procedures made to extract high-quality literature to answer the questions posed above was conducted as follows. First, a search in relevant databases to find peer-reviewed articles were made. A search with the keywords depression, SSRI and tianeptine were made in three databases: PsychInfo (n = 87245), Web of Science (n = 17) and PubMed (n = 66). The search was made between the fourth and the 14th of February. Since the search in PsychInfo with the selected keywords gave a large number of hits (n = 87245), the search was filtered to find the most relevant articles of the past five years. To be sure that only the most relevant articles were chosen, inclusion and exclusion criteria were composed. A second search to find newly published articles were made on April 11th. No relevant articles meeting the inclusion criteria and comparing the effects of tianeptine against SSRI had surfaced (see Figure 1).

The inclusion criteria to find the most relevant articles was to only include research and literature which used participants with major depression, moderate depressive disorder or bipolar disorder type II, tianeptine or different kinds of SSRI needed to be compared with each other or with placebo, but preferably with each other. Randomization to conditions was preferred. Animals studies were also included in the study to give an insight into the neurochemicals and mechanisms antidepressants act upon. The exclusion criteria for articles was depression among elderly treated in a nursing home, as there is a degeneration of neurons and potentially other underlying conditions of the elderly brain. Literature using tianeptine and SSRI in trials having little to do with depression, and literature not giving enough information about the treatment and effect of the antidepressants used was also excluded.

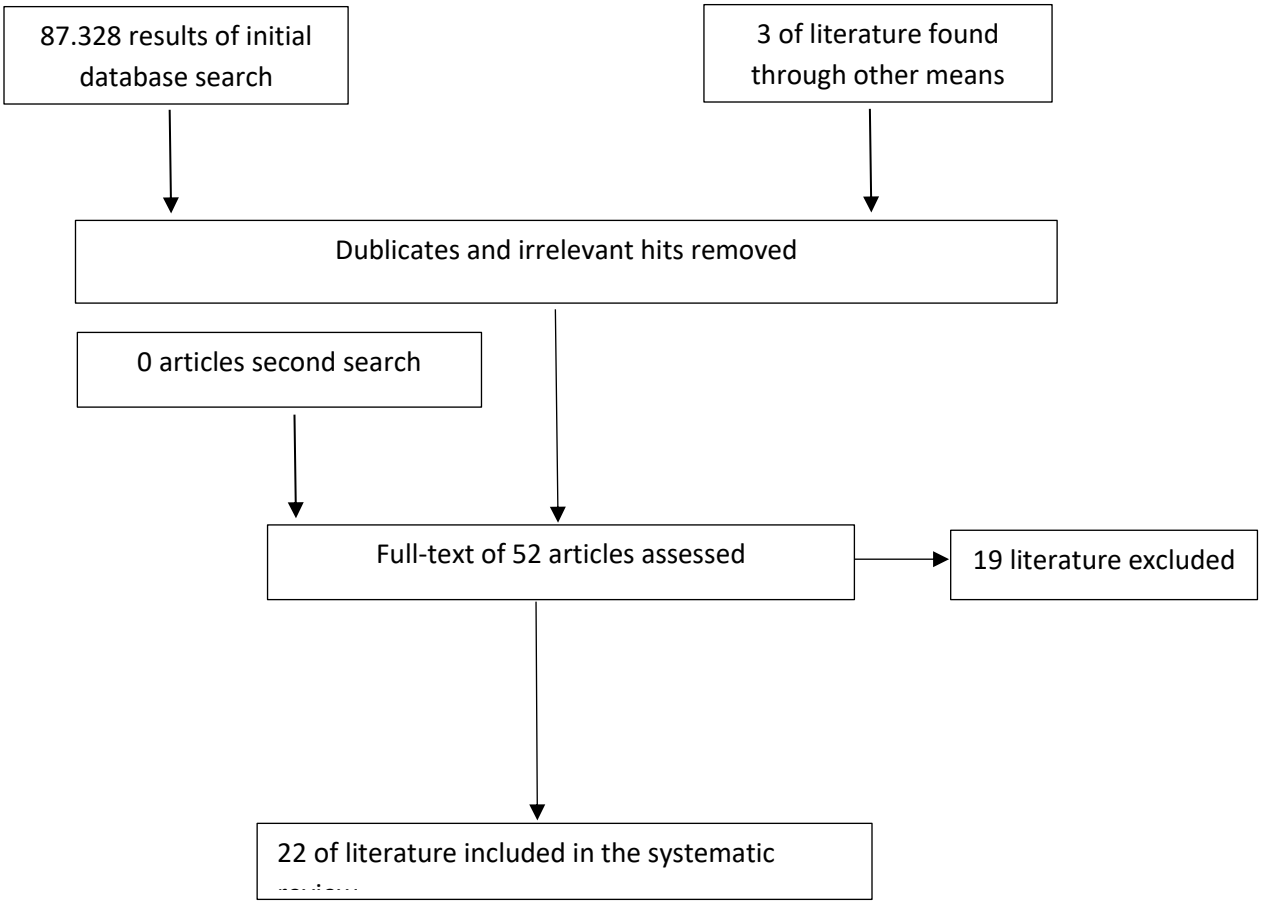

Figure 1. Flow diagram summarizing the literature search.

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To avoid any kind of publication bias, even pre-published research which meets the inclusion criteria and with a well-designed method was included. To eliminate as much bias as possible a study design which consider the sample size, control of variables, the objectives of the researcher and the conflict of interest of the research was pursued. The results are

presented with research investigating the mechanisms and neurochemistry first followed with the study which aims to examine the efficiency and lastly the studies focusing on the side-effects.

Results

From the initial search, 22 articles were included and 19 articles were excluded after evaluation of the full texts. This section will present and objectively critique the results from the literature search. The tables are made to provide an overview of all the studies used in this thesis. The tables present the author followed by the aim, study design and the measures and statistics used and finally, a rough presentation of the results and the significance level is presented. It should be used to grasp the importance of each study in a convenient manner.

Mechanisms and Neurochemistry

The neural mechanisms and neurochemistry SSRI and tianeptine act upon are interesting since earlier literature show that the serotonin hypothesis of depression might not be as evident as previously thought. SSRI and tianeptine act differently on the serotonergic system and have been noticed in previous research. This raises questions of what similarities and differences these agents have which produce their antidepressant effects. What happens in the depressed brain when given these agents? This section explores the mechanisms and neurochemistry affected by SSRI and tianeptine by presenting research which aims to investigate this phenomenon. Can stress induced alteration in the brain which causes depressive-like behaviour be reversed or changed by tianeptine and SSRI?

Mutlu et al. (2012). With the aim of investigating the effects of tianeptine and fluoxetine in mice exposed to unpredictable chronic mild stress (UCMS) (Mutlu et al., 2012). Mice were exposed to UMCS even in the behavioural test period. After two drug-free weeks and exposure to UMCS, mice were semi-randomized to condition groups. During five weeks the mice were either administered tianeptine, fluoxetine or vehicle. After UMCS exposure, mice were tested on the splash test, the resident-intruder test, the tail suspension test, the novelty suppressed feeding test and stress hormones and proinflammatory cytokines changes were measured (Mutlu et al., 2012).

The splash test revealed that stressed mice groomed a lot less compared to non-stressed mice. Antidepressant treatment with both tianeptine and fluoxetine showed to significantly increase the grooming behaviour of stressed mice (Table 1). Even in the resident-intruder test

a significant difference was observed between the groups, in which stressed mice displayed an increased amount of attacks compared to non-stressed rats. Both tianeptine and fluoxetine showed to significantly reduce aggressive behaviour (Table 1). The tail suspension test showed that stressed mice displayed a significantly enhanced immobility than non-stressed mice. This immobility was significantly reduced by both tianeptine and fluoxetine (Table 1). In the novelty suppressed feeding test no difference between stressed and non-stressed mice was seen in latency of eating food. Although fluoxetine and tianeptine both reduced the latency (Mutlu et al., 2012). The levels of the hormone ACTH and the cytokines IL-6 and TNF-α which are increased during stress were significantly reduced by fluoxetine and tianeptine (Table 1).

By staining cells with bromodeoxyuridine (BrdU) showed that stressed mice had no BrdU stained cells in the hippocampus and degenerated cells could be seen in the hippocampus and dentate gyrus. This indicates that stress mice show signs of atrophy of neurons in this area. Mice treated with tianeptine and fluoxetine had more BrdU cells than non-treated stressed animals but fewer than non-stressed animals. Chronical treatment with tianeptine showed to increase both density and the number of newly generated cells in the hippocampus (Table 1) (Mutlu et al., 2012).

Mice with UCMS have shown to have diminished grooming behaviour and induce immobility in rats during stressful events. Both fluoxetine and tianeptine increased the grooming behaviour and reduced the immobility in mice with UMCS. The fur quality of these mice is worsened due to their condition but a chronic treatment with either fluoxetine or tianeptine reverse the state of the fur quality caused by stress. The increase of the hormone plasma ACTH and the cytokines IL-6 and TNF-α which occur during toxic conditions are both reduced by tianeptine and fluoxetine (Mutlu et al., 2012). In mice with UCMS treated with tianeptine, a significant enhancement of BrdU stained cells could be seen. This indicates that tianeptine can help to prevent neuronal atrophy caused by stress. Mice treated with fluoxetine only showed a weak increase in the cellular distribution Mutlu et al. (2012). Tianeptine showed to significantly increase both the number and the density of neurons produced in the hippocampus of mice with UMCS. Although the effect could be seen in fluoxetine as well, it was minor in comparison with tianeptine.

This study presents the effect antidepressants have on the behavioural changes in the depressed brain. It also displays results for some of the neurochemical and structural changes antidepressants induce on the alterations caused by stress. As mentioned in the introduction,

the serotonergic system is considerably studied in the past, but what other systems can be affected by these agents?

Smaga et al. (2014). The aim was to investigate the acute and chronic effect of the cannabinoid system (eCb) and the adaptive alterations made by tianeptine and escitalopram (Smaga et al., 2014). Rats were given antidepressants for 14 days before being decapitated. The brain tissue was then exposed to eCB and N-acylethanolamines (NAE) and then analysed (Smaga et al., 2014).

When chronically administered with escitalopram, an increase of the endocannabinoid anandamide (AEA) was seen in the hippocampus and dorsal striatum, decreased levels of the endocannabinoid 2-AG in the prefrontal cortex, frontal cortex and cerebellum (Table 1). An increase of 2-AG was seen in the hippocampus and dorsal striatum and increased levels of the endocannabinoid palmitoylethanolamide (PEA) in the hippocampus but reduced PEA in frontal cortex and cerebellum (Table 1). Acute administration showed no changes in levels of AEA. Acute administration showed decreased levels of 2-AG in the frontal cortex, levels of PEA in frontal cortex and cerebellum and decreased the endocannabinoid oleoylethanolamid (OEA) levels in the frontal cortex and cerebellum (Table 1). After the washout period, an increase of AEA levels was noticed in the hippocampus, the 2-AG levels in the hippocampus and dorsal striatum increased, the PEA levels decreased in the frontal cortex and cerebellum and decreased levels of OEA in the frontal cortex and cerebellum (Table 1) (Smaga et al., 2014).

Chronic treatment with tianeptine showed an increased level of AEA in the hippocampus and in the dorsal striatum, increased levels of the 2-AG frontal cortex, decreased levels of PEA prefrontal cortex and hippocampus and reduced levels of OEA in the prefrontal cortex. No alterations could be seen in acute treatment in terms of AEA, 2-AG or OEA levels but a decrease in PEA levels was seen in the hippocampus (Table 1). After the washout period, AEA level was restored to pre-treatment levels, 2-AG levels decreased in the frontal cortex, the PEA levels decreased in the prefrontal cortex and increased in the nucleus accumbens and the OEA levels increased in the nucleus accumbens (Smaga et al., 2014).

A proposition that these medications act on another system than the serotonin one, the cannabinoid system surface based on the difference of mechanisms the antidepressants act upon and still relieving symptoms of depression. In this study, the eCb system is investigated due to the proposition that this system could be associated with the pathogenesis of depression and involved in the efficiency of antidepressants (Smaga et al., 2014). A longer period of

exposure of antidepressants showed changes in the hippocampus and dorsal striatum, where there was an increase of cannabinoid levels. When escitalopram and tianeptine treatment was terminated the alteration caused by the agents remained after 10 days of non-drug exposure. It can be due to the antidepressants effect on the cannabinoid system in the striatum which causes a decrease in symptoms (Smaga et al., 2014).

These results display similarities such as increased levels of AEA in the hippocampus during chronic treatment and no alterations of AEA in acute treatment are noticed. Although, the results show mostly differences in the alterations of neurochemistry and the affected mechanisms between these agents. There is a collection of research which tries to find the mechanisms these agents act on in the brain and the alterations caused by them. A systematic review is trying to combine the research to gain insight into the matter (Uzbay, 2008).

Uzbay (2008). A review discussing the effects of tianeptine on neuroplasticity found that literature describing animal testing has shown that tianeptine increases damaged dendrites to return to their normal lengths, while fluoxetine did not (Uzbay, 2008).

In vivo measures with proton magnetic resonance spectroscopy has shown that the neuroaxonal marker of the neuronal function and capacity and a decrease of the cells energy substrate, the creatine and phosphocreatine (Cr), and the important component of the cell membrane and the choline (Cho) levels (Table 1). This decrease can be the cause of impaired synaptic plasticity and by monitoring these three could be a predictor of efficiency of antidepressants (Table 1) (Uzbay, 2008). Rodents exposed to chronic stress have shown to have less BrdU stained cells which indicate that there is a significant decrease in neurogenesis in stressed rodents (Table 1). Results from two different studies indicate that these impairments of neuroplasticity can be restored by treatment with tianeptine. It has been seen that other kinds of chronic treatment with antidepressants such as SSRI has enhanced cyto- and neurogenesis in the dentate gyrus (Uzbay, 2008). When administered with the chronic treatment of tianeptine the apoptosis caused by stress was reduced in the temporal cortex and hippocampus but not in the granular layer of the dentate gyrus and the cornu ammonis of the hippocampus (Table 1).

There are certain genes such as nerve growth factor (NFC), the membrane glycoprotein 6a (M6a), GNAQ and CLK-1 which have been found to be associated to neuroplasticity and the transcript levels of these have shown to be reduced in rodents exposed to chronic stress. Tianeptine has shown to restore the changes in the effect stress caused on the genes. The levels of phosphorylated CREB (pCREB), BDNF mRNA and protein in the hippocampus and

amygdala can be regulated by tianeptine in rats with chronically restrained stressed. Tianeptine have shown to reduce the levels of pCREB while increasing the levels of BDNF and the neurotrophic factor expression in the amygdala (Table 1) (Uzbay, 2008).

Acute injection of 20mg tianeptine or fluoxetine in the nerve pathways between the prefrontal cortex and hippocampus 40 min before electric stimulation interrupt reduction of excitatory postsynaptic potentials (EPSPs) caused by stress. No significant difference was seen from solely the drugs in absence of electrical stimulation which suggest that the changes could be due to synaptic plasticity, in particular to long term potentiation (LTP) impaired by stress (Table 1). Compared to fluoxetine, tianeptine showed a longer lasting effect on the stress-induced LTP changes (Table 1) (Uzbay, 2008). Although there are contradictory findings to the effect of tianeptine on the LTP changes caused by stress and that tianeptine is inefficient in these matters. The anxiolytic effects of tianeptine is also challenged due to supporting evidence both in favour and against the theory of its anxiolytic properties (Table 1).

Most studies investigated in the review of Uzbay (2008) is conducted on animals and there are a limited number of articles assessed. Nor does it point out the method nor a give a thorough description of the results of the data and the results and discussion should thus be taken lightly from this kind of review. The author does point out an interesting case when he suggests that after evaluation of the data presented a neuroplastic hypothesis should be considered according to tianeptine rather than a monoamine one. SSRI is not as helpful in restoring the decreased neuroplasticity caused by stress in the depressive brain as tianeptine as shown by these results. Although SSRI does enhance the cyto- and neurogenesis. Even in this study differences in the effect of the neurochemistry and mechanisms of both agents. Since both SSRI and tianeptine both aid neuroplasticity, can both of them also affect the auditory fear conditioning and the underlying mechanisms of these in the depressive brain?

Burghardt et al. (2004). A study investigating the effects of citalopram and tianeptine during the acquisition auditory fear conditioning using adult rats (Burghardt, Sullivan, McEwen, Gorman, & LeDoux, 2004). The study was a four-way study designed with either administration of tianeptine or citalopram, acute or chronic administration. In the acute condition, rats were given one injection one hour before training. Rats in the chronic condition were administered one injection the day before training (Burghardt et al., 2004).

Rats were introduced to an unconditioned stimulus (a tone) which was combined with an unconditioned stimulus (foot-shock). After the conditioning phase, the rats were tested

without any injection of agents and the behaviour was observed. Fear was measured in the number of seconds freezing (Burghardt et al., 2004).

Rats in the acute citalopram group showed an increase in auditory fear conditioning and a shorter acquisition phase. When compared with the control group, the results from the acute citalopram suggests that rats injected with citalopram were freezing more than the control group (Table 1). The results showed that acute injection of tianeptine did not display any significant difference in freezing compared to the control group (Table 1). Animals chronically administered with citalopram did not display a difference in their freezing behaviour compared to the control group. In the drug-free day, rats who had been chronically treated with citalopram showed decreased freezing behaviour compared to the control group (Table 1). The authors of the study propose that the reduced freezing seen in the drug-free trial is a result of chronic administration of citalopram in which memory consolidation is affected (Burghardt et al., 2004). During acute injection with citalopram an increase of auditory fear conditioning could be seen (Table 1).

In the treatment group with chronically administered tianeptine, rats showed no significant difference in freezing behaviour compared with the control group even though they showed difficulties during the acquisition phase (Table 1). The results suggest that there could be difficulty during the acquisition phase since these rats show significantly less freezing behaviour (Burghardt et al., 2004). During the drug-free day, this difficulty was seen as well.

The fact that tianeptine failed to show an anxiogenic effect combined with earlier results of the effects of tianeptine might suggest that tianeptine could be especially desirable in some cases. Both citalopram and tianeptine have shown to be efficient in treating depressive symptoms, although both seem to have implications regarding memory and learning. When investigating the effects of tianeptine and SSRI during auditory fear conditioning gives a decent insight into the effects of these agents on the mechanisms involved in this process. Fear conditioning is well-known conditioning with distinctive brain areas involved such as the amygdala which is also known to be involved in anxiety disorder (Burghardt et al., 2004).

The mechanisms of anxiety are partly an overactive amygdala. Auditory fear conditioning also shows the heavy involvement of the amygdala and tianeptine is more efficient in decreasing these symptoms based on these results. Citalopram does not have a prominent anxiolytic effect as tianeptine does and the mechanisms it acts upon in auditory fear conditioning are different from tianeptine's. The results also show interesting findings regarding the effect they have on memory and learning in which both seems to have

consequences on the mechanisms behind these processes. They both shows to be efficient in treating symptoms although side effects cannot be discussed widely by these results. What molecular alterations do the agents have in brain areas in the stressed induced depressive brain?

Patrício et al. (2014). The aim of this study was to investigate the alteration in dentate gyrus caused by UCMS and the effects of antidepressants on these alterations in rats. Mice were then exposed to UCMS for six weeks and the last two weeks rats were injected with tianeptine or fluoxetine (Patrício et al., 2014).

Anhedonia was assessed by the sucrose consumption test (SCT) and was assessed at baseline, week four and six and the sweet drive test (SDT) was conducted during week six. Forced swim test (FST) was made at the end of UCMS exposure. Corticosterone levels were measured in the blood of the rats and morphological analysis was made. After 24h of the last injection, the rats were killed and the dentate gyrus was examined (Patrício et al., 2014).

The results showed that stressed rats had a decreased craving for sucrose solution in the sucrose consumption test (SCT) both at week four and at week six and this effect was reduced by all the four antidepressants used in this study (Table 1). Stressed rats also showed less preference for sweet pellets than control rats, and tianeptine and fluoxetine showed to increase the preference for sweet pellets. Even the immobility seen in stressed rats during the forced swim test was reduced with tianeptine and fluoxetine (Table 1). The increased latency during the novelty suppressed feeding test seen in stressed rats were also reversed by the two agents (Table 1). The disruption of the corticosterone levels seen in stressed rats was also reversed by the antidepressants (Patrício et al., 2014).

Both antidepressants reversed the significantly shorter granule cells in the dorsal dentate gyrus. The number of regulation of transcripts was 93 in stressed rats and 209 transcripts were altered by fluoxetine, and 293 of tianeptine. The results showed that fluoxetine distinguished by enhancing the gene expressed neurons while tianeptine did not show an enhancement of a particular cell type (Patrício et al., 2014).

Antidepressants repaired the damage to the dendrite branching in the dorsal dentate granule cells of the hippocampus caused by stress. It was noted that at the beginning of a depressive-like behaviour the effects of an antidepressant of the neurogenesis in the hippocampal dentate gyrus were small between experimental groups (Table 1). The authors continue by suggesting that the small impression is due to the remaining mature cells in the tissue in contrast to the small number of progenitor cells which caused a weak representation

of neurogenesis in the hippocampus. Fluoxetine also showed to be involved in downregulating pro-inflammatory response pathways genes. Tianeptine showed to downregulate stress-induced neurotoxins and thus regulating a number of genes such as those involved in drug metabolism, DNA damage response and biosynthesis (Patrício et al., 2014).

Tianeptine and SSRI are both involved in the alteration of transcripts changed by the UCMS as well as the corticosterone levels. The difference this study shows in the mechanisms tianeptine and SSRI act upon is that fluoxetine acts primarily on gene expressed neurons while tianeptine does not display an enhancement of a particular cell type. Tianeptine was also distinguished from SSRI by downregulating neurotoxins. The results also show the efficiency of both agents by decreasing the depressive symptoms. There are alterations seen in the dentate gyrus made by these agents, could there be more alterations in the hippocampus than noted in this study?

Seo et al. (2014). Seo et al. (2014) carried out a study with the aim to investigate the antidepressants effect on the expression of synaptic proteins and dendritic growth in the hippocampus of rats. To cause hippocampal cell death in the brain of the rats they were deprived of B27. The antidepressants used in this study was escitalopram, fluoxetine, paroxetine, sertraline (all SSRI) and tianeptine. Brain cells were cultured with either of antidepressants and control cells were cultured without antidepressants (Seo et al., 2014).

Changes were seen in the brain-derived neurotrophic factor (BDNF) and the protein PSD-95 by the antidepressants. Significant individual effects of the antidepressants could be seen in both PSD-95 and BDNF levels as well as in B27 deprivation. the antidepressants which had a significant effect during the B27 deprivation was escitalopram and tianeptine (Table 1). It was noted that a decrease to 37% of PSD-95, 38% of BDNF and 31% of SYP was caused by B27 deprivation. All doses of escitalopram, paroxetine and sertraline significantly weakened the decrease in PSD-95 levels caused by B27 deprivation. The same effect was seen in 1μM of fluoxetine while tianeptine significantly increased the PSD-95 levels and none of the antidepressants showed an effect in control conditions (Table 1). The decrease in BDNF levels observed by the B27 deprivation was prevented with escitalopram, fluoxetine, paroxetine and sertraline (Seo et al., 2014).

All antidepressants investigated in this study significantly increased the hippocampal dendritic outgrowth during the control conditions (Table 1). All antidepressants except for imipramine diminished the decrease in dendritic outgrowth caused by B27 deprivation. It could be seen that the increase of dendritic outgrowth made by antidepressants can be

inhibited with KN-93 and H-89, although they did not alter the effect of tianeptine. This indicates that tianeptine is independent of CaMKII and PKA signalling, whereas the other antidepressants investigated are in fact dependent on these protein kinases to increase the dendritic outgrowth. The PI3K inhibitor LY294002 was shown to block the effect of all antidepressants (Table 1). PI3K can thus be yielding the antidepressant effect on dendritic growth in the hippocampus (Seo et al., 2014).

Whether antidepressants contribute to neural growth an increase in protein levels has been investigated in rodents. The authors found that antidepressants enhance neural growth and protein levels such as PSD-95, BDNF and SYP but also increases dendritic growth in the hippocampus with a B-27 deficiency by acting on enzymes such as CaMKII, PKA and PI3K. It also concluded that a range of antidepressants, among them tianeptine and a number of SSRI was enhancing the expression of the signalling protein BDNF during stressful conditions (Seo et al., 2014). It should be noted that SSRI also enhanced this protein expression during the control condition as well, while it is suggested that it is only during toxic conditions this effect is seen with tianeptine. The effect on the BDNF expression is seen in a range of mechanically different antidepressants it may not be involved in changes of serotonin systems. A positive correlation can be seen between the protein PSD-95 and the number and length of dendritic spines. This, in turn, gives an increase in synapses and enhance the synaptic signalling in the hippocampus according to a hypothesis proposed by Seo et al. (2014). Although, tianeptine seemed to increase dendritic growth mainly through the enzyme PI3K. The increase in the protein SYP in hippocampal cells deprived of B-27 propose that the antidepressants enhances presynaptic activity and the loss of it coincide with diminished hippocampal plasticity (Seo et al., 2014).

The similarities in mechanisms and neurochemicals the agents work on are the increase in the dendritic outgrowth in the hippocampus, the blockade of their effect by the LY294002, the increase in BDNF levels during stress and the increase in protein levels during B-27 deprivation. The differences of their effect on mechanisms are tianeptine's independence of certain protein kinase. Some SSRI can enhance certain proteins during control conditions.

Summary. The results of the neurochemistry and mechanisms which tianeptine and SSRI act upon are presented by the research posed above. To summarize their findings, there seems like it is not only a difference in their involvement of the serotonergic system which differences them. They seem to act differently on the cannabinoid system, monoaminergic system and also on the cytokines and protein levels in the brain. They seem to act differently

on brain areas such as the hippocampus, PFC, cerebellum and dentate gyrus and increase or decrease different neurochemicals in these areas as well. The similarities which can be found between these two according to the results are the enhancement neurogenesis in the hippocampus during chronic treatment and increased levels of anandamide, decreased levels of hormones and TNF-α levels as well as cytokine IL-6. Although can these similarities be enough to explain the antidepressant effects of these agents? It seems like these results give a challenge in the field of antidepressants, the enigma of the origin of mechanisms of the antidepressant effect might be able to give more insight into the depressive brain and how it operates. There are many alterations in the brain caused by SSRI and tianeptine, although these do not provide support for the efficiency the agents have on reducing the depressive symptoms. Therefore, the next section will present research which examines the efficiency and the side-effects of SSRI and tianeptine.

Table 1

Effect of tianeptine and SSRI on brain mechanisms and neurochemistry

Authors	Aim of the study	Study design	Measures	Results
Mutlu et al. (2012)	Effect of chronic use of tianeptine and fluoxetine in mice exposed to UMCS	Semi-randomized animal study *n*=8 / group tianeptine 5 mg/kg fluoxetine 15 mg/kg	Splash test resident intruder test tail suspension test novelty supressed feeding test measures of proinflammatory cytokins ANOVA Tukey's post-hoc test α=.05	tianeptine + fluoxetine = ↑grooming (p<.05), (p<.001) ↓ aggression (p<.001) ↓ immobility (p<.001) ↓ latency (p<.01) ↓ACTH and IL-6 (p<.01) TNF-α was ↓ (p<.01), (p<.05) ↑ BrdU stained cells in hippocampus and dentate gyrus tianeptine ↑ density and newly generated cells in hippocampus(p<.05)
Smaga et al. (2014).	Investigate the acute and chronic effect of the eCb system and the adaptive	ex vivo Animal study *N =48* rats	Examination of brain and brain tissue after	Escitalopram Chronic treatment ↑ AEA hippocampus

alterations which could be seen after consuming these agents	10mg/kg Escitalopram *n* = 24 10mg/kg Tianeptine *n* = 24 Single administration (*n*=8) Chronic administration (*n*=8) Chronic administration w. 10-days washout period (*n*=8)	Acute; Decapitation 24h after last injection Chronic; Decapitation 24h after last injection Washout; Decapitation 10 days after last injection Anandamide levels ANOVA Student *t*-test Dunnett's test α=.05	(p<.05), dorsal striatum (p<.05) ↓2-AG (p<.01), frontal cortex (p<.01) cerebellum (p<.05) ↑2-AG hippocampus (p<.05), dorsal striatum (p<.05) ↑PEA in hippocampus (p < .001) ↓ PEA frontal cortex (p < .001), cerebellum (p < .001) Acute ↓2-AG levels frontal cortex (p < .05), ↓PEA frontal cortex (p < .001), cerebellum (p < .001) ↓OEA frontal cortex (p<.001), cerebellum (p<.001). washout period ↑AEA in hippocampus (p < .05) ↑2-AG in hippocampus (p < .05), dorsal striatum (p < .01) PEA ↓frontal cortex (p < .001), cerebellum (p < .01) OEA ↓frontal cortex (p<.001), cerebellum Tianeptine Chronic treatment ↑AEA hippocampus (p<.05) dorsal striatum (p<.01), ↑2-AG frontal cortex (p < .05) ↓PEA prefrontal cortex (p < .05) hippocampus (p <

				.001) ↓OEA prefrontal cortex (p<.01). Acute treatment No alteration in AEA, 2-AG or OEA PEA ↓hippocampus ($p < .001$). Washout period AEA restored to pre-treatment levels 2-AG ↓ frontal cortex ($p < .001$) PEA ↓ prefrontal cortex ($p < .01$) PEA ↑nucleus accumbens ($p < .001$) OEA ↑ nucleus accumbens (p<.01)
Uzbay (2008)	A review discussing the effects on neuroplasticity and the benefits of tianeptine found that literature describing animal testing has shown that tianeptine ↑s damaged dendrites to return to their normal lengths, while fluoxetine did not	Review study	*In vivo* BrdU staining Biomarkers	NAA, Cr, Cho ↓during stress Tianpetine Neuroplasticity impairment restored, apoptosis ↓ in temporal cortex SSRI enhance cyto-neurogenesis in dentate gyrus Tianeptine pCREB ↓BDNF ↑neurotrophic factor expression in the amygdala ↑
Burghardt et al. (2004)	Investigating the effects of citalopram and tianeptine during the acquisition auditory fear conditioning using adult rats	four-way study designed acute condition one injection one hour before training	Fear measured by observing freezing behaviour ANOVA, *t*-test	Citalopram group Acute ↑auditory fear conditioning shorter acquisition phase

	Chronic condition one injection the day before training for 21 days 22nd day injection given an hour before training Rats introduced to the environment Two-paired training Condition stimuli (tone) paired with unconditioned stimulus (foot-shock) Rats tested without any injection of agents and the behaviour was observed 10 mg/kg tianeptine or 10 mg/kg citalopram	significance level of $p < .05$	↑freezing *t*-test, time of freezing $p = 0.018$ Chronic no significantly differences in freezing compared with the control group Drug-free day Chronic treatment ↓ freezing 11.81, $p < .01$ Tianeptine Acute No significant freezing compared to the control group $t(18) = 1.$ Chronic no significant freezing ($t(24) = .92$) and the paired shock ($t(24)= 1.51$) difference between chronic treatment and the control group (10.48, $p < .01$), tone (22.31, $p < .01$) and interaction (7.74, $p < .02$ Drug-free day significant effects for both tone (16.45, $p < .01$) and group (11.30, $p < .01$) but not for interaction (.67) *t*-test confirmed the significantly less freezing observed in the chronic tianeptine treatment

				group ($t(24) = 3.36$, $p < .01$)
Patrício et al. (2014)	Investigate the molecular effects of antidepressants on the effects of the changes in dentate gyrus caused by uCMS	randomly assigned (n=8-12/ group) stressed and non-stressed vehicle rats exposed tianeptine 10mg/kg fluoxetine 10mg/kg imipramine 10mg/kg agomelatine 40mg/kg Rats exposed to uCMS, six weeks Week 5 and 6 rats injected with antidepressants After 24h of the last injection the rats were killed and the dentate gyrus was examined	Sucrose consumption test assessed at baseline, week four and six Sweet drive test conducted week six Forced swim test was made at the end of uCMS exposure Corticosterone levels measured in the blood Morphological analysis Cohen's d for t-test (d) eta-squared for ANOVA α=.05	Stressed rats had a ↓craving in SCT both at week four (p=.045) and at week six (p=.0043) Reduced by all the four antidepressants (p=.0003). Tianeptine and fluoxetine ↑ preference for sweet pellets (p=.0018). Immobility in FST ↓by tianeptine and fluoxetine (p=.0006) ↑latency in NSF test (p=.0003) in stressed rats reversed by both antidepressants (p<.0001). Both agents reversed the shorter granule cells in the dorsal dentate gyrus (p=.0040).
Seo et al. (2013)	investigate the antidepressants effect on the expression of synaptic proteins and dendritic growth in the hippocampus of rats	Animal study B-27 deprived to cause cell death Control animals no antidepressants escitalopram 1, 10, and 50μM fluoxetine 0.1, 1 and 10μM	Measures of PSD-95 BDNF SYP ANOVA Scheffe's test α=0.5	Escitalopram and tianeptine significant effect (p<.05), ↓ levels to 37% of PSD-95, 38% of BDNF and 31% of SYP was caused by B27 deprivation (p<.01). All doses of escitalopram, paroxetine, sertraline weakened the ↓ in

	paroxetine 0.1, 1 and 10μM sertraline 0.05, 0.1 and 1μM imipramine 0.1, 1, and 10μM tranylcypromine 1, 10, and 50μM tianeptine 10, 50, and 100μM	PSD-95 (p<.05 or p<.01) and with 1μM fluoxetine (p<.001) Tianeptine significantly ↑PSD-95 levels (p<.001) BDNF ↓ prevented with escitalopram, fluoxetine, paroxetine and sertraline (p<.001). All agents significantly ↑hippocampal dendritic outgrowth (p<.006 for sertraline, p<.001 for the rest) Both agents prevented the ↓ in dendritic outgrowth caused by B27 deprivation LY294002 blocked the effect of all agents (p=.001 for escitalopram, p=.016 for fluoxetine, p=.036 for paroxetine, p=.005 for sertraline, p=.009 for tianeptine

Abbreviations ↓= decrease, ↑= increase, ↔ = no significant difference, BrdU = Bromodeoxyuridine, FST = Forced Swim Test, NSF = Novelty Supressed Feeding Test, BDNF = brain derived neurotrophic factor, NAA = N-Acetylaspartic acid, AEA = anandamide, PEA = Phenethylamine, OEA = Oleoylethanolamine, ANOVA = analysis of variance, α=.05 = significance level

Efficiency and Side-Effects

There is literature showing the efficiency of SSRI while others point to a more hesitant result. Tianeptine aside from its deviant serotonin effect might be as efficient in decreasing the depressive symptoms. When prescribed with antidepressant treatment, side-effects can emerge in the beginning or along the treatment period. Some are durable and mild while others can be adverse and more serious. The discomfort is not the only issue of side-effects,

the patient's compliance to the treatment could also be affected by them. This section will explore the efficiency and the side-effects of tianeptine and SSRI.

Murck et al. (2003). This section presents the EEG patterns during sleep of patients with MDD and how the patterns during the treatment with antidepressants appear. Sleep disturbances have like mentioned above been seen in participants diagnosed with MDD (Gazzaniga et al., 2016).

This study aimed to investigate the differences seen in the electroencephalogram (EEG) pattern during sleep of depressed patients due to different medications and if these patterns can be associated with treatment response (Murck et al., 2003). Patients with MDD were treated with either tianeptine or paroxetine and the only co-prescribed medication allowed was chloral hydrate and somatic treatment (Murck et al., 2003).

Before the study patients had to be drug-free for at least one week except for medications like fluoxetine and irreversible monoamine-oxidase inhibitors which required eight weeks of a washout period. A psychopathology assessment was made at day 1 and then every seventh day, and an EEG investigation of sleep was made on day seven and 42. A HAMD scale was used to assess levels of depression and response rate (Murck et al., 2003).

No global effect of time nor age was found. During treatment, a significant reduction of intermittent wakefulness (IW) was displayed by a univariate analysis. The factor drug displayed a great significance with paroxetine showing a lower and less rapid-eye-movement (REM) density and sleep during and more IW compared to tianeptine (Table 2) (Murck et al., 2003). REM parameters showed an association of drug and time but no association with the factor gender. Univariate analysis showed that compared to males, females had a significant increase in slow wave sleep (SWS) and a longer REM latency (Table 2). While tianeptine did not display any interaction of the factors, paroxetine showed a trend in time and displayed changes in REM density, REM sleep duration and amount of wakefulness (Table 2). Although this measure was made at day seven and the researchers believe that it could possibly be a result of baseline or as a result of the agent. Only REM density distinguished responders from non-responders when MANOVA was calculated, the paroxetine group also showed a correlation of reduced HAMD score and increased REM density, while the tianeptine group showed no such findings (Table 2) (Murck et al., 2003). Male responsive participants showed a decrease in the higher sigma frequency range of non-REM, while this could not be seen in male non-responders nor female participants. This study also showed that male participants responded better to tianeptine while female participant seemed to respond better to paroxetine.

Tianeptine and paroxetine showed to be equally efficient overall, although paroxetine seemed to be more efficient in females. Tianeptine showed no effect of REM sleep while paroxetine showed effects of similar to previous findings (Murck et al., 2003).

The agents showed a fairly difference in the mechanisms of sleep they act upon. Although, as mentioned in this study, EEG waves are different between the genders and are very different between healthy subjects and depressed patients. The overall goal of this study was to determine the treatment response by looking at the EEG patterns produced by the effect of the antidepressants. The findings show interesting results of tianeptine's effect on non-REM sleep in male participants. This is intriguing because it shows that tianeptine might actually act on different mechanisms in men compared to women. This study also confirms the effects of both agents.

Nobile et al. (2018). By conducting a study on outpatients with depressive disorder, the aim was to investigate whether tianeptine could have a lower risk of suicide ideal (SI) worsening in the beginning of the treatment. Second, if tianeptine reduced SI after six weeks of treatment regardless of antidepressant response. Third, tianeptine would after six weeks of treatment lower depression scores and increase remission rates of suicidal patients with a depressive disorder. Participants was prescribed an antidepressant in either class of SSRI or a tricyclic agent (TCA), the most frequent antidepressant prescribed was tianeptine (Nobile et al., 2018).

Patients depression was assessed by the hospital anxiety and depression scale (HADS-D) at the beginning of the experiment and after six weeks. Montgomery-Åsberg depression scale (MÅDRS) and Hopelessness scale scores were assessed at week 1, 2 and 6 to determine SI (Nobile et al., 2018).

The results showed that SSRI and TCA significantly increased the SI compared to tianeptine, although when adjusted for confounding variables only TCA showed this increased risk of SI (Table 2). Tianeptine showed to significantly decrease the SI score more compared to TCA. The association between type of prescribed antidepressant at the beginning of the study and remission rate of depression at week six (Nobile et al., 2018). When faced with the test of which antidepressant that reduces the suicidal ideation in patients with a depressive disorder, tianeptine seem to have a significantly better effect in reducing these symptoms compared to SSRI (Table 2). Although a naturalistic study showed the superior effect of tianeptine when the latter assessment was made to reduce and control for confounding variables this upper hand of tianeptine seemed to no longer be found. It is believed that due to the mechanisms of which tianeptine acts upon which diminish the

suicidal symptoms (Table 2). Nobile et al. (2018) propose that tianeptine acts on an opioid system and that it is due to the influence on this system which gives tianeptine its therapeutic effect in depressive disorders. While other antidepressants such as SSRI may cause an increase of suicide ideation in depressive patients, tianeptine seems to be less likely to produce such symptoms when prescribed (for an overview of the study and results see Table 2).

Tianeptine is proposed here to act on the opioid mechanisms and as a result, give a therapeutic effect of depressive disorder. Although, this is just a hypothesis by the authors and needs to be investigated further to be confirmed. These results show that when the matter of SI worsening tianeptine might actually be a better option compared to SSRI. Even though a second adjustment did not show an increase of SI worsening, tianeptine still showed to decrease this factor. SSRI and tianeptine are still efficient in treating depressive symptoms, but tianeptine seems to have an advantage in treating suicidal symptoms. Side-effects were not the main investigation of this study, even though suicide ideation could be seen as a side-effect this thesis proposes it as a symptom of depression. This conclusion is drawn from the symptoms to start with and not as a result of the medication treatment as the main aim of the research. SI worsening is just one of many symptoms which accompany depression, can tianeptine and SSRI be efficient in treating the overall symptoms as well?

Novotny and Faltus (2002). A study by Novotny and Faltus (2002) aimed to investigate the efficiency and safety of tianeptine and fluoxetine in patients with the depressive disorder for six weeks. In this study, they used 190 patients which were either prescribed tianeptine or fluoxetine.

The results showed a significant time effect in improved MÅDRS score from baseline to six weeks of treatment (Table 2). A difference between time and type of treatment did not show a significant difference though. Both tianeptine and fluoxetine showed to be efficient which was displayed by the percentage of responders, which were 75% in the former and 67% in the latter (Table 2). Clinicians' Global Impression scale (CGI) item 1 scores also showed a significant time and treatment effect. There was only a difference the last day of treatment in the advantage of tianeptine between treatment groups in CGI item 1 score (Table 2). The CGI item 2 test showed only a significant time effect but failed to display significant treatment and time × treatment interaction effect (Table 2). There was no significant difference in the number of side effects seen between the two groups (Table 2). The most frequent adverse side-effects seen among the groups was gastric discomfort, nausea, vomiting, dry mouth,

headache and tremors. No significant difference between the groups regarding compliance was noted (Novotny & Faltus, 2002). The results showed that of six-week administration of tianeptine and fluoxetine to participants with depressive disorders showed no significant distinction in terms of efficiency between the two agents. Both agents showed decreased the depressive scores measured by CGI. Although, tianeptine showed to promote a slightly better CGI severity on the last day of treatment and more efficient in treating symptoms of anxiety. The most frequent side effects seen during a study of six-week treatment with tianeptine and fluoxetine were headaches to the first and gastrointestinal to the latter (for an overview of the study and results see Table 2) (Novotny & Faltus, 2002).

These results suggest that SSRI in forms of fluoxetine are equally efficient in treating depressive symptoms rated on different depressive scales. Tianeptine showed a small advantage in treating symptoms of anxiety. Aside from the beneficial effect of anxiety provided by tianeptine, both agents seem to be safe to use in the treatment of depression with no adverse side-effects found in this study. The results show that the antidepressants are efficient in treating depressive symptoms, but can they also reduce the sleep disturbances in these patients?

Waintraub et al. (2002). A study which investigated the indirect effect of tianeptine and paroxetine on sleep (Waintraub, Septien, & Azoulay, 2002). A number of 277 patients diagnosed with MDD was examined in this study. Patients either received tianeptine (*n*=138), paroxetine or capsules of placebo. If clinically crucial zopiclone or bromazepam was prescribed. Patients were assessed with the MÅDRS, HAMD and the CGI scale on the first day, the seventh day, day 21, 42 and at day 90 (Waintraub et al., 2002).

It was shown that the MÅDRS score was significantly decreased in both groups in which no statistical difference was found between the tianeptine and paroxetine group. A decrease in HAMD score with no statistical difference between the groups was observed as well (Table 2). Even in the delay response seen in MÅDRS showed no significant difference between the groups nor did the delay response in HAMD score show a significant difference either (Table 2) (Waintraub et al., 2002). In terms of safety, 23.4% of patients in the tianeptine group and 26.6% of patients in the paroxetine group experienced adverse side-effects, although no significant difference was observed between the groups nor was there a difference in serious side-effects. The most frequent mild side-effects reported was nausea, headache, vomiting, drowsiness, abdominal pain and insomnia. The mean participation time

showed a statistically significant difference with an advantage for tianeptine (Waintraub et al., 2002).

When comparing tianeptine to the SSRI paroxetine there seemed to be no significant differences between the two antidepressants in the number of side effects at first glance. Although, when further investigation were made whether the side effects were actually caused by the antidepressants and not by a confounding variable a significant difference was seen in favour of tianeptine. In this study there were three participants who attempted suicide by drug overdose and one participant who showed suicidal tendencies, all four treated with paroxetine. According to the authors of the study, withdrawal and compliance of studies with antidepressants may be linked to the efficiency of the drugs in which favour towards tianeptine could be seen in mean participation time (Waintraub et al., 2002).

During the three-month period, a co-prescription of benzodiazepine to relieve symptoms of anxiety could be distributed, and no significant difference could be seen in the prescription of benzodiazepine between the two groups. Even the prescription of hypnotic drugs to aid the sleep disturbance which may accompany depression showed no significant difference in prescription between the groups. Even though this study is a relatively long-term trial (Table 2) the results and findings should be evaluated with caution since no control group was present (for an overview of the study and results see Table 2) (Waintraub et al., 2002).

Tianeptine and paroxetine are shown to be equally efficient in treating depressive symptoms during a three-month trial. In the number of side-effects, there seemed to be no difference at first glance, although at closer inspection tianeptine showed to have a slight advantage. Since SSRI is more widely studied than tianeptine, a study which compares the efficiency with tianeptine with placebo can show the efficiency in contrast to a control group.

Costa e Silva et al. (1997). With the aim to compare the efficiency of tianeptine towards placebo Costa e Silva et al. (1997) prescribed tianeptine or placebo to participants. The participants had to fulfil certain criteria of depression on the MÅDRS scale. The researchers allowed co-prescription of benzodiazepines in some (Costa e Silva et al., 1997).

The results of this study showed that the MÅDRS score at the end of the study was significantly lower in the tianeptine group and decrease of 56.8% compared with the placebo group with a decrease of 44.5% of participants completing the study (Table 2). Tianeptine also showed to be more efficient than placebo when measured with the CGI item one and two scales, although it should be noted that no difference was seen in item 3 on the scale (Table 2). No difference could be noted between the two conditions on the Hamilton anxiety rating

scale (HARS). No difference was seen in the Zung depression self-rating scale, although in the visual analogue scale there was a difference which benefits tianeptine (Table 2) (Costa e Silva et al., 1997). The statistically significant side-effect which differed between the groups was more frequent reported headaches in the tianeptine group. No differences were seen between the groups in matter safety measures such as blood pressure, heart rate and body weight (Costa e Silva et al., 1997). The complaints noted in the tianeptine group was interrupted sleep, difficulties in falling asleep and decreased appetite and there was a low number of participants discontinuing the study due to adverse side-effects. This study confirms the efficiency of tianeptine as compared to placebo. The results from the CGI item score showed that the subjective feelings of improvement were significantly greater in the tianeptine group. The Zung depression self-rating scale showed results close to non-depressed individuals in both groups (Costa e Silva et al., 1997).

Tianeptine is proven efficient in this study when compared with placebo. When compared with placebo the only significantly more frequent side-effect was headaches in which headaches are not classified as an adverse side-effect. Tianeptine is shown to reduce depressive symptoms in the study presented above, could tianeptine and SSRI be combined and co-prescribed and still give the same efficiency?

Öztürk et al. (2004). In two case studies presented by Öztürk, Eraslan and Kayahan (2004) they describe how tianeptine relived some of the patient's depressive symptoms while paroxetine enhanced the symptoms when co-prescribed with tianeptine. In the first case, a 44-year old woman with depressive symptoms participated. She had a history of depressive episode 15 years before the resent test and was during this period treated with 75 mg/day with amitriptyline and scored 27 on the 17-item HAMD scale. Due to feelings of sedation and improved symptoms she stopped taking the prescription of amitriptyline during her first depressive episode. The second case was a 28- year-old woman which noticed her first symptoms after a family crisis six months earlier. Her HAMD score at the beginning of the study was 23 and she had no history of previous psychiatric illnesses (Öztürk et al., 2004). They were given tianeptine three times a day with a dosage of 37.5 mg a day. After four weeks she reported that some of the 44-year-old woman's symptoms had improved to a small extent (Table 2). Although she reported sustained feelings of depression, she had a slightly improved concentration and less anxious feelings. Her HAMD score had decreased to 18 and she scored 3 on the CGI scale (Table 2). The 28-year-old woman reported that she felt no relieved in symptoms, although her HAMD score was 16 and a CGI score of 3 (Table 2).

Together with the tianeptine dosage held constant, a prescription of 20 mg of paroxetine a day was added, but already after two weeks of treatment complaining that some of her the 44- year-old woman symptoms such as anhedonia and guilty feelings being worse. The tests showed a higher score on the HAMD now scoring 22, and on the CGI scale, she now scored 5 which is significantly worsened (Table 2). The 28-year- old woman also showed worsened symptoms after two weeks and scored 23 on the HAMD scale and 6 on the CGI scale which is significantly worse (Table 2). The treatment was discontinued and they were then given 125 mg of clomipramine a day and only mild side effects were noted such as retardation and some troubles of anhedonia was seen in the 44- year old woman. After four weeks on clomipramine, her HAMD score decreased to 8 and her CGI score showed 2. After the four weeks of clomipramine the 28- year-old woman only showed mild side effects such as dry mouth and palpitation, her HAMD score was 10 and CGI score 2 a huge improvement. The patients showed a decrease in the HAMD scale with 50 % already after four weeks of treatment with tianeptine (Öztürk et al., 2004). These case studies should be taken cautiously since it is two case studies it is difficult to generalize the findings to a broader population. Even though the findings suggest that in some cases co-prescription of tianeptine and paroxetine might worsen the symptoms of depression more controlled and randomized studies are needed to confirm the results (Öztürk et al., 2004). This study shows a decrease in depressive symptoms on depressive scales when treated with tianeptine. Although, when self-rated the patients seemed sceptic to the efficiency of the medication. When investigating the effect of co-prescribing SSRI and tianeptine the efficiency is very low. No side-effects regarding tianeptine or co-prescription of agents were investigated here. Impaired neurocognitive functions and increased levels of anxiety is also common in depressed patients. How efficient can SSRI and tianeptine be in patients with MDD with comorbid anxiety?

Yoo et al. (2015). Yoo et al. (2015) conducted a study on middle-aged participants diagnosed with MDD with the aim to investigate whether symptoms of anxiety and improvement in neurocognitive functions during clinical trials correlated. Participants either received tianeptine or escitalopram. The only co-prescribed medication allowed during the experiment was benzodiazepines and the dosage had to be constant at least two weeks before the beginning of the trials. No significant difference in prescribed benzodiazepines was seen between the treatment groups and a two weeks wash-out period before the study was conducted on participants who used non-approved medication (Yoo et al., 2015). To evaluate

symptoms of anxiety the HAMD and the depressive symptoms by the HAMD-17 and the cognitive functions by the mini-mental state examination test and assessments were made every fourth week. The results were corrected by a Wilcoxon signed rank and then reduced by Bonferroni correction.

The results showed that in the first stage of treatment improvement of cognitive impairments such as delayed memory and reasoning ability was positively correlated with relief in symptoms of anxiety (Table 2). Although it was noted that some neurocognitive functions did not improve when the symptoms of anxiety did, such functions were immediate memory and commission error (Table 2). Yoo et al. (2015) propose that in middle-aged patients diagnosed with MDD anxiety symptoms might be a result of subjective cognitive impairment and is a factor which can be treated. The results of this study suggest that patients with MDD with comorbid anxiety symptoms have a deteriorated memory and executive functions. It also showed that the retrieval of recently learned information becomes disturbed and process of cognitive control becomes suppressed by the anxiety symptoms (Yoo et al., 2015).

The main findings in this study were that these impaired cognitive functions due to anxiety symptoms can be relieved by treatments of antidepressants in patients with MDD. The limitations of this study were among other improvements in tests due to repetition, although practice was made in before the first test as an attempt to make participant perform good form the beginning. Another limitation was follow-up rates, although they were significantly different in the groups. The third limitation was potential researcher bias since the researcher was not blind to the conditions. The co-prescription of benzodiazepines might be a limitation since the drug might interfere with the procedures (Yoo et al., 2015).

The symptoms of MDD with comorbid anxiety can efficiently be treated with antidepressants. Some of the cognitive impairments which can accompany depression are shown to be improved by the antidepressant treatment of both tianeptine and SSRI. The response rate of an antidepressant treatment can be individual, some patient responds better to a certain antidepressant than others. What is the efficiency of co-prescribing tianeptine to an ongoing SSRI treatment of patients who are partly- or non-responsive to SSRI treatment?

Woo et al. (2013). This study aimed to investigate whether tianeptine could be efficient and tolerable in patients who slightly respond or are non-responsive to SSRI. Participants with MDD was assessed with the HAMD scale and a score of ≥14 and showed low responsiveness to SSRI. Tianeptine was co-prescribed to patients ongoing SSRI treatment. Benzodiazepines

and hypnotics were allowed by a remark from the researcher. To measure safety and efficiency the MÅDRS, HAMD and CGI-S were conducted on the participants (Woo et al., 2013).

The mean HAMD score was significantly decreased after six weeks of treatment. A significant decrease from 27.1 ± 7.3 to 12.7 ± 7.5 was seen in mean MÅDRS score after six weeks (Table 2). No significant difference between the low and high dose groups could be seen in MÅDRS and HAMD. There was a significant interaction in predicting the dose and predicting response in MÅDRS but no significance in the interaction was noticed in HAMD (Table 2) (Woo et al., 2013). The response rate of treatment seen in HAMD score was significantly different between the low and high dosage group after two weeks, and also in MÅDRS score in week four and six in favour of high dosage group (Table 2). Logistic regression analysis showed that the high dose group had a four times greater probability in remission of HAMD scores at the end of the study, although no such logistic regression could be based on MÅDRS (Table 2) (Woo et al., 2013).

In terms of safety, no significant difference could be seen between the groups. Headaches, Nausea, vomiting and sedation was the most frequently occurring side effects (Woo et al., 2013). For patients who do not respond well to an antidepressant treatment (so-called treatment-resistant), an increase of efficiency can be made by combining two structurally different antidepressants. When prescribed antidepressants in form of SSRI combined with a tricyclic agent, individuals with MDD with low response rates to treatment seem to significantly increase the effectiveness of the antidepressants. Prescribing tianeptine as an addition to an SSRI treatment for individuals non-responsive to solely SSRI have shown to increase the responsiveness in up to 65% of individuals with treatment-resistant MDD. Monotherapy, the combination of two structurally different antidepressants could be used as an effective treatment for patients suffering from treatment-resistant MDD (Woo et al., 2013).

In patients who are non-responsive or partly responsive to the treatment of SSRI, a co-prescription of tianeptine can yield the efficiency of their treatment. A higher dosage of tianeptine is correlated with a higher response rate compared to a lower dosage. In terms of safety, no adverse side-effects were noticed and only mild side-effects were frequently noted by co-prescription of the agents.

El-Shafey et al. (2016). Males diagnosed with a depressive disorder have often an erectile dysfunction (ED), El-Shafey et al. (2006) investigated the efficiency of tianeptine in males experiencing ED in the treatment of a depressive disorder. In a randomized, double-

blind, placebo-controlled study men experiencing erectile dysfunction and confirmed the diagnose through the brief sexual inventory and completed the anxiety and depression scale was studied during 16 weeks. Participants were either given tianeptine or placebo and were informed to return to ordinary sexual activity. Among men who suffer from some kind of sexual dysfunction related to the depressive disorder treated with tianeptine, a negative correlation between the depression scores and changes in the Brief Sexual Inventory score was noted. Follow-ups were made every month in which patients answered anxiety, depression, brief sexual inventory and quality of life and erection questionnaires (El-Shafey et al., 2006).

Already after eight weeks, symptoms (except for ejaculation) was significantly improved in the tianeptine group compared to the placebo group (Table 2). Evaluated by the global assessment question 89.4% of participants, 72.7% in the tianeptine group and 27.9% in the placebo group rated themselves as having improved their abilities of sexual intercourse. The results displayed a significant correlation of changes in the brief sexual inventory and the anxiety depression scale which suggests that alterations of ED are strongly correlated with alterations in symptoms of depression (Table 2). This could be seen regardless of the treatment received (El-Shafey et al., 2006). By improving the level of depression, the erectile dysfunction in men decreased and tianeptine have shown to be an efficient treatment of depression meanwhile improving the erectile dysfunction in these patients. According to the results, men with depressive disorder and comorbid sexual dysfunction did not only improve their erectile dysfunction but also their overall sexual satisfaction such as desire when treated with tianeptine. Although sexual dysfunction in depressive disorder showed improvement when treated with tianeptine, premature ejaculation was one such sexual dysfunction which was not improved during tianeptine treatment (El-Shafey et al., 2006).

This study shows that when SSRI is prescribed as an antidepressant treatment and gives unwanted side-effects in forms of sexual dysfunction, tianeptine can relieve these symptoms as well as improving the depressive symptoms. Tianeptine is thus not associated with sexual dysfunction in the degree in which is noticed in SSRI. Sexual dysfunction is not the only side-effect observed with antidepressant treatment, but which antidepressant produce the more frequent side-effects?

Kasper and Olié (2002). A meta-analysis concluding studies with over 1300 participants showed that tianeptine and SSRI seem to have an equal efficiency rate, although

SSRI seems to produce more unwanted side-effects. Studies included used tianeptine, sertraline and fluoxetine (Kasper & Olié, 2002).

The results from the meta-analysis showed no significant difference between the efficiency of tianeptine and SSRI (Table 2). The analysis assessed side-effects by clinical global impression score (CGI), item 3 which rate a therapeutic effect based on the side effects in which tianeptine showed to have a significant advantage in one of the studies (Table 2). This meta-analysis showed that tianeptine nor SSRI are significantly superior to one another in terms of efficiency. Although when the matter of side-effects tianeptine is favoured since it showed fewer side-effects compared to SSRI measured by the CGI scale item 3 in two studies presented. This effect was not seen in rats receiving tianeptine (Kasper & Olié, 2002).

This analysis shows SSRI and tianeptine to be equally efficient in treating depressive symptoms. SSRI and tianeptine showed no difference in significantly produced side effects except for one item on the score, in which tianeptine showed an advantage. SSRI is widely studied and the side-effects are fairly known but what is the frequency of side-effects of tianeptine compared to placebo then?

Cassano et al. (1996). Tianeptine shows a lower number of side-effects when compared to the tricyclic agent imipramine and placebo. As shown by a study aiming to show tianeptine's efficiency as an antidepressant. It was conducted on 186 participants diagnosed with MDD in six centres around the world. Patients were treated with placebo for seven days before the double-blind design were randomly given either tianeptine or placebo. They were also assessed by the MÅRDS every seventh day (Cassano, Heinze, LÔO, Mendlewicz, & Sousa, 1996).

Tianeptine showed to be more efficient in treating depression compared to placebo (Table 2). It has also been shown that tianeptine is a safer option of an antidepressant compared to imipramine (a MAO inhibitor), and tianeptine showed to be as safe as placebo in one a double-blind study, with reference to the low number of side-effects and discontinued treatments (Table 2). There have been no known failures in haematological parameters nor in liver values and renal functions when treated with tianeptine (Table 2). Although, tianeptine and placebo both have shown to have high enough scores on clinical tests to be considered as clinically significant. Even so, tianeptine has shown to be more efficient than placebo (Cassano et al., 1996).

These results show the efficiency of tianeptine in the treatment of depression. It also showed that tianeptine is a safe antidepressant treatment with only a low number of mild side-

effects noticed. Above sexual dysfunction is explored in men with MDD who are treated with SSRI, even though this is also common in women. The sexual dysfunction noticed in depression can be sustained or worsened by treatment with SSRI, but can this side-effect be alleviated by tianeptine?

Atmaca et al. (2003). This study investigated if patients diagnosed with MDD experiencing sexual dysfunction as result of their antidepressant treatment would become alleviated of their symptoms if treated with tianeptine instead (Atmaca, Kuloglu, Tezcan, & Buyukbayram, 2003). An inclusion criterion was that participant would have been treated with an antidepressant for at least four weeks and experiencing sexual dysfunction caused by their antidepressant. To ensure that the sexual dysfunction was not a result of another factor than the cause of antidepressant, fasting glucose levels, urine sample, complete blood count, sex hormones and prolactin level were gathered (Atmaca et al., 2003).

Participants antidepressant caused sexual dysfunction was determined by a semi-structured interview, the antidepressants consumed by the participants in which caused the sexual dysfunction was all clomipramine, paroxetine, sertraline and fluoxetine. Participants current treatment was discontinued with a wash-out period and tianeptine three times a day was prescribed. The only concomitant treatments allowed was behaviour therapy and benzodiazepines. Evaluation of sexual functions was made by the Arizona sexual experience scale (ASEX) and depression was measured with the HAMD and the CGI-I at week four and eight (Atmaca et al., 2003). The most occurrent sexual dysfunction experienced by the patients in their original antidepressant treatment was decreased libido (47.8%), erectile dysfunction (38.9% of the men), delayed orgasm or ejaculation (21.7%), anorgasmia or absence of ejaculation (13.1%) and lubrication problems in one female patient (Atmaca et al., 2003).

A paired *t*-test showed a significant difference of the HAMD score from the beginning of the study and week four and week eight and it also displayed a significant difference of the ASEX scale from baseline to week four and week eight (Table 2). No correlation was seen in a decrease of HAMD and ASEX score. Measured by the CGI-I scale 72.7% of patients were responders, none of the participants withdrew due to side-effects, although one withdrew due to becoming pregnant (Table 2) (Atmaca et al., 2003).

The limitations of this study include a small sample, it was not a double-blind study where participants could be randomized. Sexual dysfunction can be seen as one of the

symptoms of depression and it is therefore hard to control if the dysfunction was caused by the antidepressants or as a result of the depressive disorder (Atmaca et al., 2003).

The depressive symptoms were significantly decreased by the treatment of tianeptine from baseline to the end of the study. This study demonstrates a decrease in side effects in terms of sexual dysfunction caused by antidepressants when treated with tianeptine.

Summary. According to the results presenting studies investigating the efficiency of SSRI and tianeptine seem to conclude that both agents are efficient in treating the symptoms of depression. Even so, when zooming out and looking at the broader aspect of the depressive symptoms, anxiety is often comorbid with depression. When bringing in this aspect tianeptine seem to be more efficient in treating these symptoms when compared to SSRI. The efficiency is not only to be considered when prescribing an antidepressant. Since the efficiency might not be worth the side-effects are given by the treatment. Therefore, the side-effects should also be evaluated and considered in the discussion of a preferred antidepressant.

The potential side-effects antidepressants such as SSRI and tianeptine can produce are presented by the results above. As displayed by these results, tianeptine can have a slight advantage compared to SSRI since it does not produce sexual dysfunction and can relieve these symptoms produced by SSRI. Tianeptine also shows a slight advantage in item 3 on the CGI scale compared to SSRI. It should be emphasized that no results displayed a significant difference between these two in the number of adverse side effects seen. Overall tianeptine and SSRI are equally safe in a matter of side-effects. Although, some could argue that tianeptine could be favoured in some cases such as experienced sexual dysfunction or therapeutic effect based on side-effects according to the CGI scale.

Table 2

The efficiency and side effects of tianeptine and SSRI in treatment of depression

Authors	Aim of the study	Study design	Measures	Results
Murck et al. (2003)	Investigate the differences seen in depressed patient's independent of medication, what patterns of their electroencephalogram (EEG) during sleep can be associated with treatment response	Double-blind study (n=44) (♀= 13, x̃ age = 49.5 ± 11.8, ♂ = 8, x̃ age = 40.9 ± 10.8)	EEG investigation of sleep HAMD-scale to measure depression ANOVA p <.05	No global effect of time (p = .113), age (p = .47) ↓intermittent wakefulness (IW) (p = <0.01)

		Diagnose MDD Tianeptine 37.5 mg / Paroxetine 20 mg/ day		paroxetine = lower and rapid REM density ↑ IW compared to tianeptine REM association of drug and time ($p < .05$) ↔factor gender Females ↑ in SWS ($p < .05$) ↑ REM latency ($p < .01$) Paroxetine trend in time ($p < .1$) and changes in REM density, REM duration, amount of wakefulness REM density distinguished responders from non-responders ($p < .05$). Paroxetine ↓HAMD score and ↑REM density ($p < .05$)
Nobile et al. (2017)	Aimed to investigate whether tianeptine could lower the risk of SI worsening in beginning of the treatment. If tianeptine reduced SI after six weeks of treatment. Third, tianeptine would lower depression scores and ↑ remission rates of suicidal patients with MDD after six weeks.	Multi-centred 6-week (n=4017) Tianeptine SNRI SSRI tricyclic agent	HADS-D MÅDRS Wald test α=.05	SSRI significantly ↑ SI compared to tianeptine (p<.0001) Tianeptine ↓ SI Type of agent and remission rate of depression at week six (p=.003)

Novotny and Faltus (2002)	Investigate the efficiency and safety of tianeptine and fluoxetine in patients with depressive disorder during six weeks	Double-blind, randomized (*n*=190) 35.7 mg/day tianeptine (*n*=94) 20mg/day fluoxetine (*n*=96)	MÅDRS CGI t-tests Cochran-Mantel-Haenszel test ANOVA chi-square tests.	time × treatment ↔ (*p*=.87) Percentage of responders Tianeptine 75% fluoxetine 67% CGI-1 time (*p*<.001) and treatment (*p*<.02) effect. The CGI-2 test time effect (*p*<.001) no significant treatment (*p*=.22) and time × treatment interaction (*p*=.86) effect
Waintruab et al. (2002)	Investigated the effect on sleep of tianeptine and paroxetine co-prescribed zopiclone to gain indirect insight of these effects	Three-month, controlled, multicentred, randomized double-blind clinical trials (*n* = 277 with MDD) 37.5 mg/day of tianeptine (*n*=138) 20mg/day of paroxetine (*n*=139) capsules of placebo	MÅDRS HAMD CGI Assessment day 1, 7, 21, 42 and 90 Chi-2 Fisher's Student's t-test Mann-Whitney α=.05	MÅDRS ↓ in both groups (*p*=.55). HAMD ↓ (*p*=.12) MÅDRS ↔between groups (*p*=.30) HAMD ↔ daily response (*p*=.65) side-effects 23.4% tianeptine 26.6% paroxetine ↔ serious side-effects (*p*=.80)
Costa e Silva et al. (1997)	Compare the efficiency of tianeptine towards placebo	Multicentre parallel group two conditions randomization (*n* = 105)	MÅDRS CGI Zung depression self-rating scale one-way analysis chi-square	MÅDRS last day significantly ↓tianeptine (16.3 ± 11.5) ↓ of 56.8% (*p* = 0.007)

		37.5 mg Tianeptine (*n* = 52) 3-4 capsules placebo condition (*n* = 53)	α=.05	Participant completing 44.5% CGI- item 1&2 Tianeptine (*p* = 0.015) more efficient than placebo (*p* = 0.042) CGI item 3↔ ↔between the two conditions in HARS scale ↔Zung depression self-rating scale visual analogue scale difference with benefits tianeptine (*p* = 0.013 Side-effect ↑reported head-aches in the tianeptine group (*p* = 0.010). ↔safety measures
Öztürk et al. (2004)	Describe how tianeptine relived some of the patient's depressive symptoms while paroxetine enhanced the symptoms when co-prescribed with tianeptine	Case-study Case 1 44-year old woman History of depressive episode HAMD score 27 Case 2 28- year-old woman No history of	HAMD CGI	Tianeptine Case 1 HAMD score 18 CGI score 3 Case 2 HAMD 16 CGI 3 HAMD 50% ↓ after four weeks of tianeptine Tianeptine+ paroxetine

		depression HAMD score 23 37.5mg/day tianeptine Co-prescription of 20 mg/day paroxetine		Case 1 HMAD 22 CGI 5 Case 2 HAMD 23 CGI 6
Yoo et al. (2015)	Investigate whether symptoms of anxiety and improvement in neurocognitive functions during clinical trials had a correlation	12-week multi-centred with randomization (*n* = 164) Tianeptine Week 1: 20 mg/day Week 2-12: 37.5 mg/day Escitalopram Week 1: 5 mg/day Week 2-12: 10 mg/day	HAMD CGI MDQ Wilcoxon signed rank test Bonferroni correction (p<.0038)	First stage ↑ cognitive impairments delayed memory, reasoning ability was positive correlated with relief in symptoms of anxiety immediate memory and commission error not improved
Woo et al. (2013)	to investigate whether tianeptine could be efficient and tolerable in patients who slightly responded or was non-responsive to SSRI	6-week multicentre *N*=150 Tianeptine 25-37.5 mg/day (*n* = 110, low dose) (*n* = 40, high dose) SSRI = constant	HAMD score, MÅRDS score, CGI-S scale chi-squared α=.05	HAMD ↓(p<.001) after six weeks of treatment (baseline 22.4 ± 5.1, after six weeks treatment 10.3 ± 5.7) MÅDRS ↓(p<.001) from 27.1 ± 7.3 to 12.7 ± 7.5 after six weeks MÅDRS significant difference between the low

				and high dose (*P*=.479) HAMD significant difference between low and high dose (*p*=.702) MÅDRS significant interaction in predicting the dose and predicting response (*P*=.008) HAMD showed ↔ (*p*=.165) High dose group had greater remission of HAMD scores (*P*=.001) Safety No difference between groups (*P*=.299)
El-Shafey et al. (2006)	Investigated the efficiency of tianeptine in males experiencing ED in treatment of a depressive disorder	Randomized, double-blind, placebo-controlled 16 weeks (*n*=68, men) 37.5 mg/day of tianeptine (*n*=36) placebo (*n*=32)	Brief Sexual Inventory scale Student's unpaired t-test Mann– Whitney U-test chi-square test α=.05	Eight weeks Tianeptine ↑symptoms (except for ejaculation) (*p*<.05) 89.4% of participants, 72.7% tianeptine 27.9% placebo rated ↑ abilities of sexual intercourse

Kasper and Olié (2002)	To provide further support that tianeptine is effective and to update earlier studies	Meta-analysis *n* = 5 studies (*n* = 1300 participants) Trial database Medline 37.5 mg/day tianeptine 50 mg/ day sertraline 20 mg/day fluoxetine	MÅDRS CGI Two-tailed confidence interval	↔ efficiency of tianeptine and SSRI (*p* = .92) CGI - item 3 tianpetine significant advantage (*p* = .05) (*n* = 1 study) side-effects: tianeptine less side-effects
Cassano et al. (1996)	To show tianeptines efficiency as an antidepressant	Multi-centred (*n* = 6) Double-blind randomization (*n* = 186) MDD placebo seven days tianeptine (from day 1-3 12.5 mg, from day 4-14 fixed doses of 25-50 mg/day) imipramine (from day 1-3 50 mg, from day 4-14 fixed doses of 100-200 mg/day) placebo	MÅDRS (every seventh day) ANOVA Greenhouse Geiser goodness of fit method Student *t*-test Chi-square test Fisher exact test non- parametric Kruskall-Wallis test α=.05	Tianeptine efficient over placebo (14 days of treatment *p* = .005, 42 days of treatment *p* = .013) Side effects Tianeptine (*n* = 16, 25%) No known failures in haematological parameters nor in liver values and renal functions when treated with tianeptine
Atmaca et al. (2003)	Whether patients diagnosed with MDD experiencing sexual dyfunction as result of their antidepressant treatment would become alleviated of these symptoms if treated with tianeptine	Open label study Participants (*n* = 23) Sexual dysfunction caused by treatment by antidepressants ≥4 weeks.	Semi-structured interview ASEX HAMD CGI Paired *t*-test α=.05	HAMD score significant difference from beginning of the study and week four (*p* < .05) and week eight (*p* < .01) ASEX scale significant

	Antidepressants cause sexual dysfunction clomipramine (*n* = 8, 150-225 mg/day) paroxetine (*n* = 7, 40.60 mg/day), sertraline (*n* = 4, 100-200 mg/day) fluoxetine (*n* = 4, 20-80 mg/day) wash-out period of fluoxetine 4 weeks other antidepressants 2 weeks 37.5mg/day tianeptine	difference from baseline to week four ($p < .05$) and week eight ($p < .01$) No correlation in ↓ of HAMD and ASEX score ($r = 0.12$, $p < .05$) Responders CGI-I scale = 72.7% responders None of the participants withdrew due to side-effects (*n* =1 withdrew, cause: became pregnant)

Abbreviations ↓= decrease, ↑= increase, ↔ = no significant difference, IW = Intermitted Wakefulness, REM = Rapid Eye Movement, SWS = Slow Wave Sleep, HAMD = Hamilton Rating Scale for Depression, MÅDRS = Montgomery-Åsberg Depression scale, SI = Suicide Ideation, SD = Sexual dysfunction, ANOVA = analysis of variance, α=.05 = significance level

Discussion

The aim of this thesis was to answer three main research questions: 1. What mechanisms and neurochemistry do SSRI and tianeptine act upon in the depressed brain. 2. To compare the efficiency of the two agents. 3. To investigate whether there is a difference in the side-effects these agents produced. There were certain main findings of this thesis such as the two agents act differently of many aspects of the brain mechanisms and neurochemistry such as the cannabinoid system, expression of different cell types and their dependence of protein kinase. Even so, the results show that both agents are equally efficient in treating the depressive symptoms in the larger context, although some interesting findings are seen when zooming in. Anxiety is often comorbid with depression and even though both tianeptine and SSRI are shown to reduce these symptoms during chronic administration, SSRI can produce an anxiogenic effect in the beginning. Another noteworthy finding was that tianeptine showed

to be clinically significant, but so did placebo. The third aim investigated the differences in side-effects between these two agents, and both agents were equally safe in the number of adverse side-effects. Though tianeptine showed to have some slight advantages in manners of sexual dysfunction and item 3 on the CGI scale.

Discussion Mechanisms and Neurochemistry

Fear conditioning is a form of conditioning in which the response is easily observed and measured, and thus often used in animal studies. It is also useful in observed response in depression since an overactive amygdala is observed in patients with depression and anxiety and fear conditioning is associated with the amygdala as well (Burghardt et al., 2004). Chronic treatment of both agents showed freezing behaviour similar to control animals and the agents showed to interrupt the fear conditioning (Burghardt et al., 2004). This means that the helpless behaviour is decreased and the animal does not simply give up in a difficult situation. It also indicates that with chronic treatment, both agents have an anxiolytic effect. The acute treatment, on the other hand, showed that in the beginning of treatment SSRI yields auditory fear conditioning by shortening the acquisition phase (Burghardt et al., 2004). These results indicate an increased anxiogenic effect in the first period of treatment with this agent. No such findings were seen with tianeptine which suggests that it has anxiolytic effect from the beginning of the treatment.

SSRI and tianeptine are shown to have both similarities and differences in the neurochemicals and mechanisms they act upon in the depressed brain. There is not only a diversity between the agents but also dose-dependent changes can be noticed. Tianeptine and SSRI both decrease the levels of the stressed induced hormone ACTH and also proinflammatory cytokines such as TNF-α and IL-6 (Mutlu et al., 2012). They both show increased cells in the hippocampus as shown by BrdU staining. Although, tianeptine show increased density and new cells in the hippocampus as well (Mutlu et al., 2012). During chronic administration, they both increase the cannabinoid AEA in the hippocampus and dorsal striatum and no alterations are seen in acute injections (Smaga et al., 2014). Both agents display similarities in their effect during B-27 deprivation, in which they diminish the decreased dendritic outgrowth caused by B27 deprivation (Seo et al., 2014). Even though tianeptine increases the PSD-95 levels reduced by B27 deprivation, SSRI only weakened this reduction. It seems like both of the antidepressants are dependent on enzyme PI3K, which is involved in cell growth (Seo et al., 2014). Both agents when injected between the PFC and the hippocampus show to reduce the EPSP caused by stress (Seo et al., 2014).

The differences between these two agents in the neurochemicals and mechanisms they act upon that BrdU staining also showed that tianeptine increased the density of the cells in the hippocampus as well (Mutlu et al., 2012). In chronic treatment, the 2-AG levels were increased in the frontal cortex by tianeptine but increased in the dorsal striatum and hippocampus by SSRI (Smaga et al., 2014). The PEA levels are increased in the hippocampus and decreased in the frontal cortex and cerebellum by SSRI while tianeptine decreased these levels in the prefrontal cortex and hippocampus (Smaga et al., 2014). Tianeptine also showed a decrease of the OEA levels in the PFC while no documented OEA levels in chronic treatment were observed by SSRI (Smaga et al., 2014).

In acute treatment, 2-AG and OEA levels were not altered by tianeptine while SSRI decreased 2-AG in the frontal cortex and decreased the OEA levels in the frontal cortex and the cerebellum. The PEA levels in acute treatment were decreased in the hippocampus by tianeptine but decreased in the frontal cortex and cerebellum by SSRI (Smaga et al., 2014). During a wash-out period, the AEA levels were restored by tianeptine and increased in the hippocampus by SSRI. The 2-AG levels were decreased in the frontal cortex by tianeptine and increased in the hippocampus and dorsal striatum by SSRI (Smaga et al., 2014). The PEA levels are decreased in the prefrontal cortex and increased in the nucleus accumbens by tianeptine while SSRI decreases the levels of PEA in the frontal cortex and cerebellum (Smaga et al., 2014). OEA levels are increased in the nucleus accumbens by tianeptine and decreased in the frontal cortex and cerebellum by SSRI. Also, the neuroplasticity during this period show differences between the SSRI and tianeptine, while the latter restore the neuroplasticity the former enhance neuro- cytogenesis in the dentate gyrus (Seo et al., 2014). The results also seem to indicate that tianeptine is independent on the protein CaMKII and PKA which usually aid the neurite outgrowth (Seo et al., 2014). The apoptosis caused by stress in the temporal cortex and hippocampus is also reduced in chronic treatment with tianeptine as well as the alterations of the protein in some genes are restored. The LTP changes last longer when treated with tianeptine (Seo et al., 2014).

Discussion Efficiency and Side-Effects

The efficiency can be seen in both human and animal studies. In animal studies, depressed rodents display alterations in stress-induced behaviour due to the antidepressant effects (Burghardt et al., 2004; Mutlu et al., 2012; Patrício et al 2014). The behaviour observed in rodents when they are stressed are among others increased aggressive behaviour to strangers, increased immobility and freezing in stressful situations and increased latency

when presented with food. These adverse behaviours caused by stress can be reversed by both SSRI and tianeptine (Burghardt et al., 2004; Mutlu et al., 2012; Patrício et al 2014). As mentioned, anhedonia is a symptom of anxiety and it is characterized by reduced motivational behaviour and lack of experiencing pleasure (Gazzaniga et al., 2016). The behaviour observed in the rodents during a stressful stimulus such as time of latency during the NSF and decreased grooming behaviour are partly caused by anhedonia. Both SSRI and tianeptine showed to reduce the latency and increase the grooming behaviour which suggests that they are relieving symptoms of anhedonia (Mutlu et al., 2012). The NFS also measure the anxiety levels of the animal, in which were also decreased along with the corticosterone levels by the antidepressants (Mutlu et al., 2012). The feelings of helplessness which accompany depression are also seen in rodents in which the immobility and freezing and discomfort during a stressful situation increases in depressive-like animals (Burghardt et al., 2004; Mutlu et al., 2012). Even in these cases SSRI and tianeptine aid in reducing the freezing and immobility and the animals try to escape the unpleasant situation.

SSRI and tianeptine also showed to reduce depressive symptoms in humans when measured with various diagnostic scales such as the MÅDRS, HAMD and CGI scale (Nobile et al 2018; Waintraub et al., 2002; Woo et al., 2013. An interesting finding was that one study showed that tianeptine is clinically significant, but so was placebo as well (Cassano et al., 1996). This raises the issue if the observed relief in symptoms could be due to a placebo effect. It is not something that can be concluded from this review since only one study mentioned this effect. This particular study also mentions that tianeptine still show to be more efficient in decreasing the symptoms than placebo (Cassano et al., 1996). Comorbid anxiety is also often present in depression. Since many studies report that SSRI has an anxiogenic effect in treatment onset (Burghardt et al., 2004; Yoo et al., 2015). Although, tianeptine show to have some advantage in the item-3 on the CGI-scale and show a slight advantage in reducing anxiety (Costa e Silva et al., 1997). Overall both SSRI and tianeptine showed to alleviate the symptoms of depression, although some results revealed that there might individual differences such as symptoms and comorbidity which could determine the best suitable agent.

Contradictory findings are discovered in regards to the different side-effects produced by SSRI and tianeptine. While many studies found no significant differences between the agents' others did (Atmaca et al., 2003; El-Shafey et al., 2006; Kasper and Olié, 2002; Yoo et al., 2015). The literature opposing the non-significant difference in their findings have shown that tianeptine has an advantage to SSRI considering side-effects (Costa e Silva et al., 1997). As seen by the results presented tianeptine has shown to relieve the sexual dysfunctions

mainly ED and also improve the overall sexual satisfaction in sexual dysfunction in men (Atmaca et al., 2003¸ El-Shafey et al., 2006). Another study supported this notion and that tianeptine improved sexual dysfunctions caused by other antidepressants. The most frequent side-effects noticed in the treatment of both SSRI and tianeptine are headaches, nausea and gastric problems (Novotny & Faltus, 2002; Waintraub; Woo et al., 2013). Although these symptoms can be uncomfortable, they do not commonly interfere with a patient's daily life as much as other more adverse side-effects. Tianeptine did not show any adverse side-effects in forms of haematological parameters, abnormal liver values or abnormal renal functions (Cassano et al., 1996) although, nor did any studies presented here report these in SSRI either. Although worsening of suicide ideation is debatable if it could be considered as a side-effect of the treatment, SSRI does show to increase these risks to a large extent in some cases (Nobile et al., 2018).

Tianeptine as an Alternative Option. In cases when patients have low responsiveness to SSRI, results suggest that tianeptine could be used to relieve the patient's depressive symptoms (Woo et al., 2013). At first glance, an increase in SI caused in treatment onset of SSRI can be avoided using tianeptine. Tianeptine is shown to produce a significant less SI worsening compared with other agents, among them SSRI (Nobile et al., 2018). Tianeptine is also less likely to produce suicide ideation at the beginning of treatment while SSRI could increase these effects (Nobile et al., 2018).

The EEG pattern during sleep of depressed patients can differ, different treatments also display differences in the EEG waves of sleeping patients (Murck et al., 2003). while it seemed that men responded better to tianeptine, females seemed to respond better to SSRI. This difference between genders in response to treatment and differences in EEG patterns of depressed patients could be due to the difference in hormones and sex steroids.

As these findings suggest tianeptine could be favoured to SSRI in some cases. SSRI can produce unwanted side-effects in the form of sexual dysfunction and findings propose that tianeptine can help alleviate these symptoms (El-Shafey et al., 2006). Depression is already a disorder which makes the affected patient withdraw from social activities and decrease in libido is noticed in the absence of treatment. When the treatment is enhancing the sexual dysfunction and among them a decrease in libido it could increase the issues of a patient's social life.

Co-prescription of tianeptine to enhance the effect of SSRI show diversity, but could be a possibility of treatment in some cases. While one finding suggests that there is actually

possible to co-prescribe tianeptine to the constant dosage of SSRI in patients who are non- or partially-responsive (Woo et al., 2013), another study suggests that it will do so up to 50% and that there are better alternatives which could be provided (Öztürk et al., 2004). Tianeptine has shown to decrease the symptoms of anxiety and to be anxiolytic already from treatment onset (Burghardt et al., 2004; Costa e Silva et al., 1997). Therefore, tianeptine should be considered in the cases in which comorbid anxiety is present in patients with MDD.

Limitations. Since this thesis focused on the mechanisms, efficiency in reducing symptoms and the side-effects no literature on the economic aspects nor the pharmacological prescription of the two antidepressants were made. Both pharmacological prescription and the financial aspects may have to do with the favoured prescription of SSRI. There has also been noted on the literature of these antidepressants, that a higher dose of tianeptine is often prescribed to obtain the desired effect could be a possibility not studied in this thesis as well, no comment can be made about this as well. There was no literature presented of research with antidepressant co-prescribed with cognitive behavioural therapy. This could be considered a limitation since cognitive behavioural therapy combined with antidepressants could reduce the relapse rate after treatment termination.

Some of the studies used a relatively small sample and a couple did not use a double-blind study design which could complicate the interpretation of data. The relatively small sample of research presented in this review is also a limitation. The limited time-period of this thesis made it difficult to evaluate a broader and more thorough search. The unknown mechanisms of tianeptine is also a limitation since this prevents further discussion of the effect of the antidepressants. SSRI compared to tianeptine is a more widely studied and comprehended agent and thus more research of its effect are present. This could provide a bias towards the efficiency of this agent since more explanations of its effect can be stated. No research on the response rate of placebo is presented in this thesis.

Implications. This thesis could aid in discussions of antidepressants in the treatment of depression and challenge some of the current hypothesis of the cause of depression. This thesis assembles a variety of studies which investigate different aspects of SSRI and tianeptine. With a high prevalence of the disorder and a relevant matter of today, this could inflate the insight into these antidepressants and contribute to an elaborate debate on the issue. It also raises issues in the relevant research and the need for future research in the field to find the most efficient treatment. Issues such as: Why are some antidepressants more favoured than others? What treatment overall is most efficient in the matter of chronic treatment and

low relapse rate? What are the mechanisms which tianeptine act upon? Answers to these issues still remain and future research on the matter is needed and essential in this field.

Future research. To be able to make an equitable comparison between the two agents more studies are needed on the mechanisms of tianeptine. Research on the preference of SSRI should be brought into the discussion. Why is this used in a broader range than other antidepressants? Should individual and gender differences be studied further to more effectively alleviate symptoms? The interesting question of how two very different agents can produce the same efficiency in depression is interesting and should be investigated further. The reduced number of researches made of tianeptine in recent years makes it hard to investigate the results further and more research on the matter should surface. The matters which should be examined further is thus, the mechanisms of tianeptine, the individual effects the two antidepressants work upon and why these two fundamentally different agents produce the relief of symptoms in depression.

Conclusion

There are similarities in how the SSRI and tianeptine act on the cannabinoid system. Both, for example, increase the levels of the cannabinoid anandamide in the hippocampus and dorsal striatum during chronic administration. They both displayed a decrease of the hormone ACTH, the levels of corticosterone and the levels of the cytokines IL-6 and TNF-α which increase during stress. The agents also showed to decrease the levels of anhedonia and reversed the transcript changes caused by stress. SSRI and tianeptine both showed to increase the dendritic outgrowth in the hippocampus. Both also showed to have an implication on memory and learning, although more research is needed to confirm this. The results showed that. The differences were seen between the two agents for example that chronic treatment with SSRI increase the levels of the cannabinoid 2-AG in the hippocampus and decrease these levels in the PFC and cerebellum. Chronic treatment with tianeptine showed to increase the levels of 2-AG in the frontal cortex. Tianeptine also showed to increase the number and density of newly generated neurons to a larger extent compared to SSRI. During auditory fear conditioning in rats, tianeptine was shown to have an anxiolytic effect from the beginning of treatment while SSRI did not. In fact, SSRI increased the auditory fear conditioning at the beginning of treatment which suggests that SSRI have an anxiogenic effect in treatment onset. The results also showed that fluoxetine an SSRI distinguished by enhancing the gene expressed neurons while tianeptine did not show an enhancement of a particular cell type.

Tianeptine also showed to be independent on certain protein kinase which the efficiency of SSRI relies on.

The results show that both tianeptine and SSRI are efficient in decreasing the depressive symptoms in numerous diagnostic scales such as the MADRS, HAMD and CGI scale. When looking at the broader context though, anxiety is often comorbid with depression and even though SSRI enhances these symptoms in treatment onset, both are shown to decrease these symptoms during chronic administration. Though it should be noted that the results suggest that tianeptine is slightly superior to SSRI in the matter of treating the depressive symptoms. Tianeptine is also more efficient in reducing suicide ideation in depressed patients. When tianeptine was compared with placebo, both interestingly showed to be clinically significant, which brings the question of placebo effect to mind.

In matters of side-effects, tianeptine and SSRI does not differ in adverse side-effects produced during the treatment course. Although, tianeptine seem to have a small advantage compared to SSRI as seen by a few factors. SSRI might produce unwanted side-effects such as sexual dysfunction, tianeptine has shown to reduce sexual dysfunction not only as a symptom of depression but also as a result of antidepressant treatment. One meta-analysis also showed that tianeptine showed a slight advantage on item 3 on the CGI scale. This element measures the therapeutic effect based on side-effects.

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