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T3 Augmentation in Major Depressive Disorder - Literature Review

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ABBREVIATIONS

Major depressive disorder (MDD), triiodothyronine (T3), thyroxine (T4), 5-hydroxytryptamine (5-HT), selective-serotonin reuptake inhibitor (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRI), monoamine oxidase inhibitor (MAOi), tricyclic antidepressant (TCA), Hamilton Rating Scale for Depression (HRSD-21).

SUMMARY

Triiodothyronine (T3), also referred to as liothyronine, is a hormone produced and secreted by the thyroid gland, as well as derived from its less-active form thyroxine. T3 augmentation refers to the use of supplemental triiodothyronine to increase the efficacy of antidepressant treatment. Its effects on the central nervous system are theorized to relate to serotonin-receptor activity, particularly serotonin 1A-, 1B- and 2A-autoreceptors. This literature review explored the pathophysiology of depression, through which the use of triiodothyronine augmentation was discussed. The applicable literature demonstrated that T3 augmentation can be beneficial in patients who gained initial benefit from the use of selective-serotonin reuptake inhibitors and tricyclic antidepressants, but did not reach remission on these drugs alone. Major limitation in the literature was the lack of studies regarding other antidepressant groups, in addition to the majority of the literature having been published over 10 years ago. With major advances in the development of neuromodulation and atypical antipsychotics, the research into T3 augmentation for depression is insufficient to favor its use over other adjunctive therapies. T3 augmentation's strength in comparison to other adjunctive therapies is its properties as an accelerator of antidepressant therapy, as well as low incidence of adverse effects. In conclusion, there is limited research on T3 augmentation in depression, and the presented literature does not offer consistent results on the efficacy of T3 augmentation. Despite T3 augmentation often being forgotten among other adjunctive therapies, it may be beneficial to a specific patient population.

KEYWORDS

Major depressive disorder, treatment-resistant depression, serotonin, monoamine, thyroid, triiodothyronine.

INTRODUCTION

Depression is a common debilitating disorder. Per current research, it is considered multifactorial in its etiology. Despite extensive research, the scientific and psychiatric communities have not yet reached a common ground on the pathogenesis of depression. For an extensive period, the treatment of depression has relied on selective serotonin reuptake inhibitors, alongside other groups of antidepressants. These include serotonin-noradrenaline receptor inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants. In addition to this, psychotherapy has been used both as a monotherapy as well as in an eclectic approach together with pharmacotherapy. Alongside these key methods of managing depression, neuromodulatory approaches have advanced in recent years. Despite the advances in managing depression, there still exists a marked population that experience treatment-resistant depression. The lack of understanding behind the pathophysiology of depression may lie behind the treatment resistance.

The monoamine hypothesis arose in the psychiatric community in the 1960s. Prior to this there were incidental discoveries regarding a drug called reserpine in the 1950s. The hypothesized role of serotonin and noradrenaline in depression was discovered through the adverse effects of reserpine. After this, the monoamine hypothesis started to develop and it was considered the most reliable theory on the pathogenesis of depression until recently. In 2022, in an umbrella study it was concluded that there is not enough evidence to state that serotonin would play a significant role in the pathogenesis of depression. This, yet again, leaves the psychiatric community without a clear answer on what exactly is responsible for the occurrence of depressive symptoms, and what is the best way to treat these symptoms. Antidepressants are widely used for treating depression, and significant benefit is often reported from their effect. In addition to this, neuromodulation has seen great development in recent years, for example with the applications of esketamine and transcranial magnetic stimulation. These treatment modalities still fail to recognize the undeniable correlation between our endocrinology and psychiatric symptoms.

In literature, a particular point of focus between endocrinology and psychiatry appears to be the function of the thyroid gland. Thyroid gland is a butterfly-shaped organ located in the anterior neck. Although depression is considered to originate from the central nervous system as all other psychiatric disorders, it also undeniably causes systemic effects, such as sleep disturbances, changes in appetite, and fatigue. In addition to this, it is important to note that

the thyroid gland functions under the regulation of the hypothalamus, which naturally is a part of the central nervous system. Based on these findings, it can be stated that although depression primarily affects the central nervous system, its symptoms also manifest systematically. This argument is further supported by the monoamine hypothesis: the same exact neurotransmitters that are considered to be the causative factor behind the occurrence of depressive symptoms also exist in other tissues. This literature review will take a closer look at the relationship between thyroid hormones and depressive symptoms, particularly on triiodothyronine and its effect on serotonin receptors.

This literature review will explore the development of the monoamine hypothesis as well as recent findings related to the serotonin hypothesis in depression. Based on these findings, this literature review will observe the relationship between depressive symptoms and activity of serotonin 1A-, 1B- and 2A-receptors, with respect to the effects of triiodothyronine hormone on these receptors. Based on the findings in the applicable literature, this literature review will aim to determine the efficacy of triiodothyronine augmentation in treatment-resistant depression. The goals of this literature review is to evaluate the use of triiodothyronine augmentation and its benefits, to discuss the relationship between depression and thyroid hormone action with respect to serotonin 1A-, 1B- and 2A-receptors, to discuss the mechanism of action of triiodothyronine augmentation in depression, and finally to compare the use of triiodothyronine augmentation with other adjunctive therapies in managing treatment-resistant depression.

LITERATURE REVIEW

1. Depression and its current treatment

Depression is a broad term that refers to a variety of affective disorders, also known as mood disorders. The focus of this literature review will be on major depressive disorder, which is characterized by unipolar decrease in mood, motivation, self-image, and performance of an individual. These are only examples of common symptoms, and patients diagnosed with major depressive disorder may exhibit a variety of characteristics. The most significant difference between different types of depression is whether the disorder is unipolar or bipolar. Unipolar depression is characterized by a mood decline from baseline, while bipolar depression is preceded, followed by or simultaneously occurring with an incline in mood. It is particularly important to differentiate between these two affective disorders in this literature

review, as they also differ in treatment.[1] This literature review will also include literature regarding bipolar depression; however, this is used to support the findings related to unipolar depression. Regardless, the emphasis will remain on unipolar depression, particularly on treatment-resistant depression.

Major depressive disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), has to include five or more of the following symptoms within a two week period when there exists a decline in the baseline mood; with addition that at least one of the symptoms has to be either depressed mood or loss of pleasure, also known as anhedonia: (1) depressed mood for most of the day, nearly every day, (2) markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day, (3) significant weight loss without attempting to lose weight, or significant changes in appetite nearly every day, (4) sleep disorders: insomnia or hypersomnia nearly every day, (5) psychomotor agitation or retardation nearly every day, (6) fatigue nearly every day, (7) feelings of worthlessness or feelings of inadequate guilt nearly every day, (8) difficulties concentrating or indecisiveness nearly every day, (9) recurrent thoughts of death, suicidal ideation or acute suicidality. In addition to these nine symptoms, the disorder should also cause significant distress or impairment in several sectors of functioning, as well as any organic and other psychiatric disorders should be ruled out.[2] It should, however, be noted that as this literature review will discuss treatment-resistant depression, the diagnostic criteria for patients with treatment-resistant depression may not follow the DSM-5 criteria. This is due to treatment-resistant depression having developed over time, with patients accommodating to their symptoms, as well as the fact that partial relief of symptoms may have been achieved with pharmacological, psychotherapeutic or neuromodulatory approaches.[3]

Treatment-resistant depression is defined as a subset of major depressive disorder, which does not respond to first-line or other traditional treatment modalities, often specifying the number of attempted antidepressant therapies to be a minimum of two. Treatment resistance may also discuss major depressive disorder that has partially benefited from traditional antidepressant therapy, but where significant residual symptoms still remain. Traditional pharmacotherapeutic management of major depressive disorder relies on antidepressants of several groups.[4] In the most widespread use are selective serotonin reuptake inhibitors, often referred to as SSRIs. Together with serotonin-noradrenaline reuptake inhibitors (SNRIs),

selective serotonin reuptake inhibitors comprise the first-line pharmacogenetic treatment of depression. The mechanism of action of both these drug groups is based on the monoamine hypothesis, which will be discussed later in this literature review. In addition to selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors, there also exists tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOi), noradrenaline reuptake inhibitors, serotonin modulators and atypical depressants.[5] With expanding information on neurotransmitter activity in depression, we are able to attempt to optimize treatment according to specific symptoms of depression. As an example, noradrenaline is thought to act on performance and indirectly on dopamine receptors. Dopamine is responsible for motivation and reward-based behavior.[6] Hence in a patient whose most significant symptoms are related to these behaviors, the first attempt at treatment can be made with an antidepressant that also has an effect on noradrenaline activity. This, due to a lack of adequate scientific evidence, still relies on individual experiences of each physician and their objective data.[7]

Although the exact pathophysiology of depression remains unknown, it has been theorized to a large extent. Since the initial discovery of monoamine neurotransmitters' effect on the occurrence of depressive symptoms, the monoamine hypothesis has been relied on to explain the development of depression. Alongside this, different endocrinological, psychological, genetic and psychosocial theories have been formulated. These theories do not oppose, but rather complement each other. The common conclusion uniting the different theories on the pathophysiology of depression is that depression is, in fact, multifactorial in its etiology. This literature review will take a closer look at themes surrounding the monoamine hypothesis and the endocrinology behind depression.

2. Monoamine hypothesis

Monoamine hypothesis was first introduced in literature in the 1960s, but the initial discoveries regarding the effect of monoamines in depression were made in the 1950s. Reserpine, originally a drug intended to treat hypertension, was found to have adverse effects that appeared clinically similar to depression. Its effects on blood pressure were caused by the inhibition of uptake of noradrenaline, a monoamine neurotransmitter. This in turn resulted in lowered levels of serotonin and catecholamines, such as dopamine and noradrenaline. Eventually, due to this discovery, reserpine was also classified as a first-line antipsychotic - a

drug that regulates the overactivity of certain dopamine tracts in the central nervous system that are considered to be responsible for the occurrence of psychotic symptoms. However, the side effects of reserpine on previously psychiatrically healthy individuals were considered significant enough to withdraw the drug from clinical use.[8]

To understand the monoamine hypothesis, it is also important to briefly discuss the different monoamine neurotransmitters. Due to the scope of this literature review, the discussion will be limited to serotonin, also known as 5-hydroxytryptamine (5-HT), dopamine, and noradrenaline. These monoamine neurotransmitters are of most significance to this literature review due to their high receptor activity in the central nervous system, unlike for example that of adrenaline - for which most receptors are found systematically outside of the central nervous system. Monoamines are divided into classical monoamines and trace amines. Serotonin, dopamine and noradrenaline all belong in the group of classical monoamines. While dopamine and noradrenaline are further classified as catecholamines, serotonin and melatonin are classified as indolamines. Catecholamines are connected by their common precursor compound, levodopa, which results in similar molecular structures between these neurotransmitters.[9] This is clinically significant when discussing treatment for Parkinson's Disease or Attention Deficit Hyperactivity Disorder, as well as when discussing treatment of depression. Indolamines are characterized by their common pathway of synthesis, particularly as melatonin is further synthesized from serotonin. Melatonin is a neurohormone, a hormone that is both produced and released by neuroendocrine cells in the hypothalamus. The effects of melatonin are of importance in regard to regulating humans' circadian rhythm, also known as our sleep-wake cycle. It is important to note that similarly to melatonin, thyrotropin-releasing hormone is also produced and released by the hypothalamus.[10, 11]

Like any process in the human body, the functions of neurotransmitters also do not exist in a vacuum. This is particularly relevant when considering the effects of neurotransmitters on the hypothalamus. Hypothalamus is responsible for producing seven hormones: corticotropin-releasing hormone, dopamine, gonadotropin-releasing hormone, growth hormone-releasing hormone, somatostatin and thyrotropin-releasing hormone. In psychiatric disorders, of particular importance are dopamine, corticotropin-releasing hormone and thyrotropin-releasing hormone. While dopamine is often overlooked when discussing the monoamine hypothesis, as there is more research and clinical evidence pointing to the role of serotonin and noradrenaline in the pathophysiology of depression, it is important to note the

conditions where dopamine may contribute to the occurrence of depressive symptoms. First of all, psychotic disorders such as schizophrenia manifest as both positive and negative symptoms. The negative symptoms have a lot of overlap with depressive symptoms, and major depressive disorder is a common comorbidity in psychotic disorders.[12] In addition to this, there exists a subtype of major depressive disorder that presents with psychotic symptoms alongside the typical depressive symptoms. Schatzberg et al. proposed in 1985 that the effects of increased corticosteroids by dysregulation of the hypothalamic-pituitary-adrenal axis resulted in changes in dopaminergic activity, which therefore is responsible for the occurrence of psychotic symptoms in severe depression.[13] This theory was revoked by Duval et al. in 2000, stating that psychotic symptoms in depression are not caused by dysregulation of dopaminergic pathways. This conclusion was based on the results of dexamethasone suppression testing and testing using a dopamine agonist called apomorphine on subjects diagnosed with depression with psychotic symptoms. The results of the clinical trial led to the understanding that changes in the hypothalamic-pituitary-adrenal axis regulation are not responsible for dopamine dysregulation in depression. It did not, however, rule out the role that the hypothalamic-pituitary-adrenal axis may play on the occurrence of depressive symptoms in general.[14] In 2017 in a literature review Belujon et al. discussed the relationship between the dopaminergic pathways and occurrence of anhedonia in depression, also highlighting the incidence of depressive symptoms in diseases characterized by low dopamine levels, such as Parkinson's disease.[15] This demonstrates the multifactorial nature of depression, and highlights the misunderstood role of dopamine in the pathophysiology of depression.

The role of the hypothalamic-pituitary-adrenal axis in major depressive disorder has been extensively researched, and this research has concluded that a relationship between increased cortisol serum concentrations and occurrence of depressive symptoms exists.[16] The role of cortisol is especially highlighted in the cognitive performance of depressed subjects in comparison to healthy controls. Poor cognitive performance was there on found to affect the remission status of these subjects, concluding that elevated cortisol levels affect the remission status of depressed subjects.[17] This is relevant to the scope of this literature review as the dysregulation of hypothalamic-pituitary-adrenal axis in depressed patients was found to be linked to serotonergic pathways through stimulation of the anterior pituitary gland by

serotonin, resulting in the release of adrenocorticotropic hormone. This finding yet again highlights the role of serotonin in the pathophysiology of depression.[18–21]

Serotonin has been the main neurotransmitter thought to be behind the pathophysiology of depression for decades. This is partially due to the positive results seen from monotherapy with selective serotonin reuptake inhibitors. Moncrieff et al. stated in their systematic umbrella review in July 2022 that there is no consistent evidence that depression would be caused by decreased levels of serotonin in the central nervous system.[22] This still leaves the question of why drugs that target to increase serotonin levels in the central nervous system are effective in treating depression. To review this further, the next subsection will be focusing on the different serotonin receptors in the central nervous system, especially on serotonin 1A-, 1B-, and 2A-receptors.

3. Clinical symptoms in relation to serotonin receptors

Serotonin was first discovered in 1935 by an Italian scientist called Vittorio Erspamer.[23] It was first studied as a vasoconstrictor, but serotonin receptors were later on discovered to exist in the central nervous system. Seven serotonin receptor subtypes have been identified in the human body. Its molecular structure is similar to that of gamma-aminobutyric acid, or GABA, another neurotransmitter that is mainly involved in inhibitory pathways in the brain. Serotonin receptors, also known as 5HT-receptors, act as both ligand-gated and G-coupled receptors. Serotonin is stored in presynaptic vesicles, from which serotonin is released into the presynaptic cleft through axonal activation due to an electrical impulse. In the presynaptic cleft, serotonin either binds to postsynaptic serotonin receptors or undergoes reuptake into the presynaptic vesicles. The effects of serotonin are caused by the neurotransmitter binding to these postsynaptic serotonin receptors. Selective serotonin reuptake inhibitors work by preventing the reuptake of serotonin from the presynaptic cleft, allowing for higher concentrations of serotonin to bind to the postsynaptic receptors. Essentially it can be stated that the effects of selective serotonin reuptake inhibitors are not due to increased concentrations of serotonin, but rather due to modulation of serotonin receptors.[24]

In the seven subgroups of serotonin receptors, 14 receptors have so far been discovered. In relation to depression, serotonin 1A and serotonin 1B receptors have been researched the most.[25] Particularly the role of serotonin 1A-receptor is highlighted in literature as being

significant in the theory behind the pathophysiology of depression, alongside serotonin 1B-receptor. In the case of serotonin 1A-receptor, literature demonstrates that serotonin receptor partial agonists are effective when used alongside selective-serotonin reuptake inhibitors. [26–29]

Serotonin 2A-receptor has been linked to both the occurrence of affective symptoms, as well as psychotic symptoms. Depressive symptoms have been linked to the downregulation of serotonin 2A-receptor, while psychotic symptoms have been linked to the overactivation of these receptors. Clinically this is relevant when considering the treatment options for depression: antidepressants, such as selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors, are thought to act on serotonin 2A-receptors similarly to their mechanism of action on serotonin 1A- and serotonin 1B-receptors. Atypical antipsychotics, such as aripiprazole, quetiapine and brexpiprazole, have been demonstrated to have an antagonistic effect on serotonin 2A-receptors alongside their effects on dopamine 2 -receptors.[30] In relation to what was earlier discussed regarding the monoamine hypothesis, there is evidence supporting the effects of antipsychotic drugs' efficacy in managing treatment-resistant depression, particularly when combining them with antidepressant therapy. This will be explored further in this literature review.

Serotonin receptor activity is characterized both by autoreceptors and heteroreceptors. Autoreceptors are receptors that respond only to the neurotransmitters that are released by the neuron on which they are lodged. They differ from heteroreceptors by the heteroreceptors' property to respond to neurotransmitters that are released from adjacent neurons. Monoamine hypothesis is often simplified to only cover the activity of heteroreceptors, while many serotonin receptors exist both as hetero- and autoreceptors.[31] In rat studies, serotonin 1A-receptor agonists have been shown to have properties similar to antidepressants.[32, 33] These findings were contributed to the drug's agonism on serotonin 1A-heteroreceptors, while it is demonstrated that the agonism of serotonin 1A-autoreceptors would result in an increase in depressive symptoms. This opposing effect is thought to be behind the delayed effects of selective serotonin reuptake inhibitors, and is explained by the eventual desensitization of these autoreceptors. Although antidepressants are not selective between hetero- and autoreceptors, there is further research into blocking the activation of these autoreceptors.[34, 35]

Despite extensive research into polypharmacy in depression, as well as evidence supporting the use of eclectic approaches in managing depression, there still exists a patient population who do not reach remission. To explore this further, in the later chapters of this literature review the effects of thyroid hormones on the occurrence of depressive symptoms and the relationship between serotonin receptors and triiodothyronine will be discussed. Based on this background knowledge, the clinical applications of triiodothyronine augmentation in major depressive disorder will be reviewed.

4. Thyroid hormones

Thyroid gland is an organ located in the anterior neck. It functions under the hypothalamus-pituitary-thyroid axis. The relevance of the hypothalamus on monoamine neurotransmitters was discussed earlier in this literature review. Similarly to melatonin, thyroid hormone synthesis is controlled by the hypothalamus through the release of thyrotropin-releasing hormone. Thyrotropin-releasing hormone stimulates the pituitary gland in a negative feedback loop to release thyroid-stimulating hormone. Thyroid-stimulating hormone responsible for the effects of the thyroid gland.[36]

Thyroid gland is responsible for producing and releasing two hormones: thyroxine (T4) and triiodothyronine (T3). In medicine the focus is mostly shifted on thyroxine, which is the main hormone responsible for regulating metabolism and energy levels.[37] Undoubtedly, the disorders involved in thyroxine overproduction or underproduction mimic or mirror the symptoms of psychiatric disorders. For example, hypothyroidism, a condition that is characterized by the underproduction of thyroxine, presents with fatigue, depressive mood, hypersomnia, trouble concentrating and weight gain. In addition to these overlapping symptoms with depression, there are other systemic symptoms present.[38] This is clinically relevant, as the diagnosis of major depressive disorder calls for excluding any organic causes of depression. Treatment wise, if the depressive symptoms were to be caused by hypothyroidism, management with thyroxine-supplementation is expected to correct these symptoms. Joffe et al. (1990) found that the response to triiodothyronine adjuvant therapy was statistically significantly higher than the response to thyroxine adjuvant therapy in depression.[39]One consideration with this is the adverse effects of excessive thyroxine, or the development of hyperthyroidism.[40] Hyperthyroidism, in turn, results in symptoms that mimic

or mirror the symptoms of anxiety: restlessness, insomnia, weight loss, and tachycardia. In addition to this, hyperthyroidism is associated with elevated mood, also known as hypomania, mania, or euphoria. It is important to note that patients presenting with primary mania, also known as mania that is not caused by an underlying physical condition, may also have subclinical hyperthyroidism as an incidental finding.[41] Hyperthyroidism is also associated with the physical symptoms of mania: psychomotor agitation, heart palpitations, and hypertension.[42] The key differentiating factor between clinical hyperthyroidism and subclinical hyperthyroidism related to a manic episode is that the overactivity of the thyroid gland returns to baseline through adequate psychiatric treatment with mood stabilizers and antipsychotics. In conclusion, there is a clear overlap between the symptoms caused by hypothyroidism and depression, and respectfully between hyperthyroidism and mania. Thyroxine is not used to manage unipolar depression, mainly as there is not enough data to support its efficacy. There, however, is significant research into the efficacy of thyroxine augmentation in bipolar depression. In bipolar depression T4 modulation has been shown to be significantly more efficient than T3 modulation.[43] In addition to this, in rat studies chronic use of thyroxine has been demonstrated to increase the amount of serotonin 2A-receptors in the brain.[44]

Triiodothyronine is a hormone derived from thyroxine, and it is both produced and released by the thyroid gland. Majority of the production of triiodothyronine occurs through conversion from thyroxine, approximately 80% of the circulating triiodothyronine. This means that if there is an underproduction of thyroxine, there is also an underproduction of triiodothyronine. Triiodothyronine is considered to be the more active form of thyroxine. The conversion of thyroxine to triiodothyronine is mediated by deiodinase enzymes. There are three types of deiodinase enzymes recognized. Majority of the conversion is carried out by type I deiodinase enzyme, which is present in the thyroid gland, liver, kidney and pituitary. This is of lesser relevance to the scope of this literature review. Type II and type III deiodinase are found in the central nervous system, among other tissues. Type II converts thyroxine into active triiodothyronine, as discussed previously, while type III converts thyroxine into reverse triiodothyronine. Reverse triiodothyronine is an inactive form of the hormone, and its significance lies in the metabolism of thyroxine. In addition to this, an important function of reverse triiodothyronine is its features in competitive inhibition of the transport molecules of thyroxine and triiodothyronine.[45]

Triiodothyronine, as discussed earlier, is found in the central nervous system. In general, the effects of triiodothyronine are the same as those of thyroxine, as triiodothyronine is simply the more active form of thyroxine. Triiodothyronine has been theorized to act on the serotonin 2A-receptor in an inhibitory pattern, through which it increases the concentrations of serotonin in the presynaptic cleft, as discussed in the paragraph regarding the monoamine hypothesis.[46] Also importantly, deiodinase type II is expressed in the hypothalamus, which is responsible for the production of dopamine, and indirectly for the release of melatonin. The role of hypothalamus in the occurrence of depressive symptoms will be explored further later in this review.[47]

The effects of low concentrations of thyroid hormones on the developing brain have been researched extensively. Thyroid hormones have been found to play a major role particularly in axonal development, and insufficient concentrations of thyroxine and triiodothyronine during the developmental period have been found to lead to mental retardation.[44] In addition to this, low levels of triiodothyronine have been found to exist in brain dead patients. However, less is understood about the direct effects of thyroid hormones on the adult brain.[48]

As discussed earlier, the symptoms of hypothyroidism mimic or mirror the occurrence of depressive symptoms. The relationship between hypothyroidism and depression has been described as bidirectional. However, there exists a large population of depressed patients who do not experience any other symptoms of hypothyroidism except for the overlapping depressive symptoms, and their thyroxine or triiodothyronine levels present as normal in laboratory testing. It is important to note that triiodothyronine is not measured in routine clinical practice. The most common indication for triiodothyronine testing is the suspicion of a disorder affecting the conversion of thyroxine into triiodothyronine. As a result, the true population of depressed patients who present with low triiodothyronine levels in the presence of normal thyroxine levels remains theoretical. One reasoning behind not measuring triiodothyronine levels routinely is that although triiodothyronine has a higher concentration of receptors in the central nervous system compared to thyroxine receptors, the current theory on the relationship between triiodothyronine and the pathophysiology of depression is explained by receptor activity rather than the concentration of triiodothyronine. According to literature, this does not mean that these patients could not benefit from supplementary thyroxine or triiodothyronine therapy. It has been proposed that the neuropsychiatric

symptoms associated with thyroid hormone action may be caused by decreased uptake of the hormones into the brain, instead of decreased levels of circulating hormones.[44, 49]

Hypothalamus-pituitary-thyroid axis is regulated through a negative feedback loop. This means that the end-products of each level of this axis also regulate the higher levels of the axis. Hypothalamus produces a hormone called thyrotropin-releasing hormone. The activity of hypothalamus, and therefore the production and release of thyrotropin-releasing hormone is regulated mainly by negative feedback through pituitary and target organ hormones. In addition to this, the hypothalamus is regulated by the concentrations of dopamine, a monoamine neurotransmitter that is produced and secreted by the hypothalamus itself, external factors (such as temperature, light, energy consumption), and cortisol levels. The release of thyrotropin-releasing hormone acts on the pituitary gland to thereon produce and release a hormone called the thyroid-stimulating hormone. Pituitary gland is thus stimulated by hypothalamic hormones, and inhibited by pituitary hormones and target organ hormones. Thyroid-stimulating hormone is responsible for stimulating the thyroid gland to produce thyroxine and triiodothyronine. Increasing levels of thyroxine and triiodothyronine go on to inhibit the hypothalamic production of thyrotropin-releasing hormone. In relation to depression, neurotransmitters (such as monoamine neurotransmitters) are responsible for the communication between the hypothalamus and other areas of the brain. Therefore, it can be stated that an imbalance in neurotransmitter activity may have an effect on the neural signaling to hypothalamus, and as a result an effect on hypothalamic activity. As discussed above, the inhibition of thyrotropin-releasing hormone will result in lower concentrations of thyroid-stimulating hormone, and eventually lead to lower concentrations of thyroxine and triiodothyronine.[50] This is a simplified explanation of the connection between monoamine neurotransmitters and the hypothalamic-pituitary-thyroid axis, but essential to understanding the use of triiodothyronine in the treatment of depression. This theory would explain the occurrence of depressive symptoms through the perspective of the overlap of depressive and hypothyroidism symptoms. Essentially this would mean that the decreased concentrations of monoamine neurotransmitters are not behind depression, but rather the inactivity of the hypothalamus. This does not, however, explain why monotherapy with thyroxine or triiodothyronine is not sufficient in managing treatment-resistant depression. The theory of neurotransmitter regulated activity of hypothalamus does help us understand the use of triiodothyronine in treatment-resistant depression. The next chapter of this literature review

will focus on the connection between serotonin receptors and thyroid hormones, leading us to eventually review the clinical applications of triiodothyronine augmentation in major depressive disorder.[50–53]

5. Serotonin receptors and triiodothyronine

The concepts of auto- and heteroreceptors were discussed in earlier chapters. Rat studies by Eitan Gur et al. in 2002 and 2004 demonstrated that triiodothyronine therapy reduced the amount of serotonin 1A- and 1B-autoreceptors in the frontal cortex. As discussed earlier, the delayed onset of antidepressant effects is thought to be due to the activation of serotonin autoreceptors, with most research delving into serotonin 1A-receptors.[54, 55] These autoreceptors are thought to have their effects through increased release of serotonin by the neuron that these receptors are embedded in. The increased neuronal firing resulting from inhibited reuptake of extracellular serotonin by heteroreceptors would potentially result in further activation of autoreceptors. This could result in eventual decrease in neuronal activity, as regulated by the autoreceptors. These features are considered to be of genetic nature, contributing to the individual response to selective serotonin reuptake inhibitors on polymorphism of the gene expression of serotonin receptors.[56] The effects of triiodothyronine on the central nervous system are largely believed to be based on the regulation of gene expression, which lays a strengthened understanding to the effects of triiodothyronine and antidepressant combination therapy.[57, 58] Yin et al, (2015) concluded that polymorphism of DRD4 gene had a statistically significant correlation with response to selective-serotonin reuptake inhibitor therapy in depressed subjects.[59]

Serotonin 1A-receptor is closely associated with the presence of symptoms of depression and anxiety. Its receptors are mainly located in the raphe of the brainstem.[60] Postsynaptic serotonin 1A-heteroreceptors have been demonstrated to exist in high concentrations in the hippocampus, prefrontal cortex and amygdala.[61, 62] Serotonin 1A-autoreceptors are somatodendritic receptors, and through a negative feedback loop they downregulate the neuronal firing rate, through which their activation eventually results in decreased concentrations of extracellular serotonin. Similarly, the activation of serotonin 1B-receptors, located in the axonal nerve terminals, reduces the release of serotonin into the extracellular space.[63] Serotonin 2A-receptor is a receptor that is expressed in the central nervous system,

at highest concentrations in the prefrontal cortex, neocortex, basal ganglia, hippocampus and amygdala. It is theorized to have antidepressant effects through its inhibition with the increase of serotonin in the presynaptic cleft, as stated according to the monoamine hypothesis. As any receptor, its activity is regulated by agonists and antagonists.[64]

Triiodothyronine is a hormone produced both by the thyroid gland and through conversion from thyroxine. Triiodothyronine functions systemically, but its significance in mental and cognitive disorders has been highlighted by its activity in the central nervous system. Majority of triiodothyronine is converted from thyroxine by deiodinase-enzymes, from which type II is the most significant in relation to its effects in the central nervous system. Type II deiodinase is found in highest concentrations in the central nervous system in the cerebral cortex, hippocampus, thalamus among other areas.[44]

According to Sandrini et al. in 1996, both acute and chronic use of triiodothyronine resulted in changes in serotonin receptors. Most significantly, without the duration of treatment being a variable, the number of serotonin 2A-receptors were found to be decreased.[65] Similar conclusions were presented by Moreau et al. in 2001, where the administration of triiodothyronine alongside imipramine, which is a tricyclic antidepressant, was found to result in decreased density of serotonin 1A- and 2A-receptors in the hippocampus of rats.[66] The key difference between these two animal-model studies was the administration of an antidepressant. Based on these findings, it can be concluded that monotherapy with triiodothyronine resulted in reduction of serotonin 2A-receptor density, while combination of triiodothyronine with a tricyclic antidepressant resulted in reduction of both serotonin 1A- and 2A-receptor density. In addition to this, Lee et al. (2017) discovered that in hypothyroid rats, the serotonin 1A-receptors in the limbic system were to have increased activity compared to euthyroid rats.[67] This further supports the bidirectional relationship between thyroid function and depression.

6. Clinical applications of T3 augmentation in Major Depressive Disorder

Triiodothyronine augmentation in depression has been shown to be most effective when combined with an antidepressant, such as a selective serotonin reuptake inhibitor or tricyclic antidepressant. Monotherapy with triiodothyronine has not been found to be an effective treatment modality. The effects of triiodothyronine in treatment-resistant depression have

been discussed to be due to increased gene expression through activating the production of thyrotropin-releasing hormone, corticotropin-releasing factor and brain-derived neurotrophic factor.[68–70]

The initial discovery of the combination of an antidepressant and triiodothyronine was made in 1969 by Prange et al.[71] In the findings of Prange et al., it was concluded that triiodothyronine was responsible for serotonin autoreceptor activation. In 2001, Altshuler et al. gathered the double-blinded studies conducted on the use of triiodothyronine and imipramine combination therapy in depression so far, and conducted a meta-analysis. The key findings of the study were that there was found to be a positive effect of combining triiodothyronine with an antidepressant, particularly early in treatment. The findings also concluded that women were more likely to benefit from the combination of triiodothyronine and imipramine.[72] Initially, the research focused on tricyclic antidepressants, such as imipramine. Later on, similar findings as in combination therapy using triiodothyronine and imipramine were found using a combination of triiodothyronine and fluoxetine, a commonly used selective serotonin reuptake inhibitor. This was described by Agid and Lerer in 2003: it was found that adjunctive therapy with triiodothyronine resulted in easing of the depressive symptoms in patients who previously did not benefit from fluoxetine monotherapy.[73] In 2007, a double-blinded, randomized study was performed by Cooper-Kazaz et al. using sertraline, another commonly used selective serotonin reuptake inhibitor, in combination with triiodothyronine.[74] The findings were similar to the studies where the response of triiodothyronine was tested together with tricyclic antidepressants and fluoxetine.[75] There, however, exists inconsistency to the previously mentioned results. Appelhof et al. found the combination of triiodothyronine with paroxetine, an older selective serotonin reuptake inhibitor, to be inconclusive in its effects. In the same clinical, trial Appelhof et al. concluded that there were more adverse effects using combination therapy of triiodothyronine and paroxetine instead of monotherapy with paroxetine.[76] There is no simple explanation as to why triiodothyronine augmentation is not effective in patients using paroxetine despite the fact that it was found to be effective in patients using fluoxetine. Although paroxetine and fluoxetine are both selective serotonin reuptake inhibitors, they differ in their receptor affinity. Paroxetine's secondary receptor affinity lies within the noradrenaline transporter, while sertraline's secondary receptor affinity involves the dopamine transporter and

fluoxetine's secondary affinity involves the serotonin 5C-receptor.[77] There is a remarkable lack of research on the use of triiodothyronine with serotonin-noradrenaline receptor inhibitors. Nierenberg et al. compared the use of adjunctive lithium and adjunctive triiodothyronine with venlafaxine, a commonly used serotonin-noradrenaline receptor inhibitor. Triiodothyronine augmentation was found to yield similar results as combination therapy of lithium and venlafaxine, however the percentage of patients who reached remission was markedly lower than in studies where the patients received triiodothyronine together with selective serotonin reuptake inhibitor.[78] Based on these findings, it can be hypothesized that the adjunctive therapy with triiodothyronine is not effective when combined with paroxetine due to paroxetine's affinity on the noradrenaline pathways. However, catecholamine depletion was found to correlate with increased triiodothyronine levels, and a positive association between T3 and T4 and depressive symptoms, which further supports the monoamine hypothesis of depression.[79]

The current understanding related to the use of triiodothyronine is based on the understanding that triiodothyronine has serotonergic effects. In rat studies, triiodothyronine alone and in combination with imipramine (TCA) has been found to reduce sensitivity of serotonin 1A- and 1B-receptors.[80, 81] These studies concluded that triiodothyronine has an inhibitory effect on serotonin 1A- and 1B autoreceptors. These autoreceptors are considered to have a long-standing effect on serotonin pathways, and their augmentation alone does not explain the positive effects of triiodothyronine adjunctive therapy in depression.[82, 83] Instead, the effect was omitted to the use of antidepressants together with triiodothyronine, where triiodothyronine modulates these autoreceptors while antidepressants have an inhibitory effect on the postsynaptic serotonin receptors. The wished effects on serotonin autoreceptor augmentation are based on the understanding that the lack of these autoreceptors increases the concentration of extracellular serotonin.[84] Moreau et al. (2000) concluded that prolonged use of antidepressants, particularly fluvoxamine, results in decreased reuptake of triiodothyronine by red blood cells.[85] This discovery demonstrates the bidirectional relationship between antidepressant therapy and triiodothyronine, as not only does triiodothyronine result in changes in antidepressant efficacy, but the use of antidepressants also modifies the activity of triiodothyronine in the organism.

Across the previously discussed clinical trials and studies, triiodothyronine was used at doses of 25-65 micrograms per day. While triiodothyronine acts in a dose-dependent matter, slight alterations in doses were found to not influence the effect of the combination therapy with tricyclic antidepressants, or with selective serotonin reuptake inhibitors.[86–88] Most significant effect of the use of triiodothyronine in managing depression was found in acceleration studies, meaning that triiodothyronine was introduced early in the initiation of an antidepressant. Particularly with tricyclic antidepressants, for the lack of research on other antidepressant groups, acceleration therapy with triiodothyronine was found to shorten the duration between treatment initiation and wished effect of the antidepressants in four out of five double-blinded studies. More relevant to the scope of this literature review are the studies that fall under the category of augmentation studies. Triiodothyronine augmentation refers to the use of adjunctive triiodothyronine with an antidepressant that has already been introduced, but where no desired effect was reached. Out of 13 studies, in 10 of these studies the augmentation with triiodothyronine resulted in over 50% of the participants responding to the combination therapy. These studies included both open and double-blind studies. These findings were concluded by Joffe in their literature review in 2011.[89–91] The results of the literature search for this literature review were mixed. Garlow et al. (2012) concluded that there was no statistically significant change in combination therapy of triiodothyronine and sertraline, with the treatment response being measured using the Hamilton Rating Scale for Depression (HRSD-21).[92] In contrast, in 2006 Abraham et al. concluded that triiodothyronine augmentation with SSRIs (including subjects on sertraline) resulted in improvement of mood scores.[93] Similarly to the study by Garlow et al., Abraham et al. also measured the response using HRSD-21. The major difference between these studies is the duration of observation: subjects in Garlow's study were observed for eight weeks, while subjects in Abraham's study were observed for a median period of 3.75 weeks. Schüle et al. (2005) found that there is no significant impact of the use of sertraline on pituitary stimulation, concluding that the therapeutic effect of sertraline is not related to the regulation of the hypothalamic-pituitary-thyroid axis activity in depressed subjects.[94] Study by Gitlin et al. in 2004 found that low thyroid-stimulating hormone levels correlated with a decrease in depressive symptoms, also measured using HRSD-21.[95] Lower baseline TSH would indicate higher thyroxine and triiodothyronine, as discussed earlier in the chapter about thyroid hormones. According to Gitlin et al., baseline TSH levels were a statistically relevant

indicator of treatment response in patients treated with SSRIs. In contrast, de Carvalho et al. (2009) found that there exists no significant correlation between SSRI monotherapy and changes in thyroid function neither on euthyroid or hypothyroid subjects. They also found that euthyroid patients treated with fluoxetine were more susceptible to minor changes in the serotonergic system than hypothyroid subjects treated with fluoxetine.[96] Finally, Gitlin et al. (1987) found no statistical improvement in depressive symptoms in patients treated with combination therapy of imipramine and triiodothyronine.[97]

The previously presented literature describes the use of triiodothyronine augmentation in depressed patients in combination with selective-serotonin reuptake inhibitors and tricyclic antidepressants. When subjecting this research into clinical practice, it demonstrates how limited our understanding of the potential of triiodothyronine augmentation is. Antidepressant groups have developed largely over the past decades, and there is no significant research on the use of other antidepressant groups alongside triiodothyronine therapy. Based on the presented literature, it can be stated that triiodothyronine therapy is definitely applicable in patients who present with depression and signs of subclinical or clinical hypothyroidism, as well as in patients who did not reach remission on selective-serotonin reuptake inhibitors or tricyclic antidepressants alone. There are large discrepancies between studies on the benefits of triiodothyronine augmentation in depression, even though the methodology of these studies is fairly similar. Most significant variable between these studies is treatment duration - shorter observation period seems to favor the benefits of triiodothyronine augmentation. This phenomenon may be explained by the acceleration effect of triiodothyronine on antidepressants. Although relevant evidence has been presented from the effects of triiodothyronine augmentation with SSRIs and TCAs, these findings do not subject to the evidence supporting the use of other combination treatment modalities' efficacy, apart from lithium. In the next chapter an overview into the most commonly used pharmacological combination treatment modalities will be presented. Due to the scope of this review, neuromodulatory and psychotherapeutic approaches have been purposefully excluded from this discussion.

DISCUSSION

In the previous chapters of this literature review, the theorized pathophysiology of depression, the relationship between thyroid hormones and depressive symptoms, the treatment

modalities, and the use of triiodothyronine in depression were discussed. According to the presented literature, it can be concluded that when the initial treatment modalities of depression are found ineffective, triiodothyronine augmentation can be compared to lithium augmentation by its efficacy in reducing depressive symptoms. Although there is promising evidence for the use of triiodothyronine in treatment-resistant depression, it is important to discuss its efficacy in context with other treatment modalities used to manage treatment-resistant depression. This chapter of this literature review will discuss the use of lithium and atypical antipsychotics in an eclectic approach to managing depression. The objective of this is to determine the benefits of triiodothyronine augmentation in relation to the adverse effects, and hence conclude whether triiodothyronine augmentation is beneficial in managing treatment-resistant depression.

Lithium is a mood stabilizer often used in the management of bipolar disorder, schizoaffective disorder, and less frequently behavioral disorders. It has been shown to be effective in managing both depressive and manic episodes.[98–100] Although lithium is an effective treatment modality, it has its limitations particularly relating to its limited dose-dependent therapeutic range and its adverse effects. The adverse effects of lithium can be divided into short- and long-term effects. Lithium therapy requires close monitoring of the patient and of lithium concentrations in the serum. Lithium has a narrow therapeutic range of 0.8-1.2 mmol/L, and exceeding this range has potentially lethal effects.[101] As a result, lithium augmentation may not be suitable for a patient who is not able to commit to frequent laboratory testing, which may limit the use of lithium in treatment-resistant depression due to the debilitating nature of the disorder. In the long term, lithium is taken up by the thyroid gland, where it accumulates and eventually results in inhibition of iodine by the thyroid. In the long-term, this results in clinical hypothyroidism.[102] In addition to this, less frequently lithium can result in hyperthyroidism.[103] This is particularly important for the scope of this literature review, as the research presented earlier discusses the relationship between hypothyroidism and depression. In addition to the adverse effects on the thyroid gland, lithium has been shown to be nephrotoxic - leading even to the development of nephrogenic diabetes insipidus.[104] Unfortunately, the thyroid and kidney changes are not reversible after the cessation of lithium therapy. In the case of hypothyroidism, supplementation therapy using thyroxine is the gold-standard treatment modality. There is a lack of research for the use of triiodothyronine supplementation in lithium-induced hypothyroidism. In 1990, Bauer

et al. discussed the use of high-dose thyroxine as a mood stabilizer.[105, 106] Their findings concluded that high-dose thyroxine may be effective when used concomitantly with mood stabilizers.[107] Theoretically, basing this assumption on the literature presented, triiodothyronine augmentation may be effective in complementing lithium therapy in treatment-resistant depression where signs of lithium-induced hypothyroidism exist. It is also important to mention that similarly to triiodothyronine therapy, the results relating to the use of lithium alongside antidepressants in treatment-resistant depression are largely based on the use of tricyclic antidepressants, and there is not enough research on other groups of antidepressants alongside lithium to conclude this to be an universally applicable treatment approach.

After antidepressants, second-generation antipsychotics are one of the most frequently prescribed drugs for treating depression. The theorized effects of antipsychotics in depression lie within the receptor affinity profile of each antipsychotic. Particularly dopamine receptor antagonism, partial agonism for serotonin 1A- and 1B-receptors, as well as antagonism for serotonin 2A-receptors, are highlighted in the antipsychotics that are approved for augmentation therapy in depression by the United States Food and Drug Administration (FDA).[108–110] The benefits of favoring antipsychotic therapy alongside antidepressants in treatment-resistant depression lie within the lesser adverse effects compared to other treatment modalities. In addition to this, there is significantly more current research on the use of antipsychotics when compared to triiodothyronine augmentation in managing depression. Antipsychotic augmentation therapy is also considered to be more cost-effective than the other treatment modalities discussed in this chapter.[111] The evidence on the effects of antipsychotics together with antidepressants is not only limited to certain groups of antidepressants, but also include research into atypical antidepressants - such as mirtazapine, vortioxetine and bupropion. Gambi et al. (2005) conducted a study on the effect of mirtazapine on thyroxine and triiodothyronine levels. In a six-month period, triiodothyronine levels increased significantly and demonstrated a positive correlation with decreased depressive symptoms.[112] The findings of these studies can be applied to the discussion of the use of triiodothyronine augmentation in concordance with atypical antidepressants. However, in relation to the scope of this literature review, the use of antipsychotics as an adjunctive therapy does not address the relationship between the hypothalamic-pituitary-thyroid axis and its overlap with the theorized pathophysiology of depression, and importantly, it does not

address the overlap of depressive symptoms with the symptoms of hypothyroidism. In contrast, atypical antipsychotics have been shown to have their effect on the hypothalamic-pituitary-adrenal axis by lowering levels of cortisol through the reduction of the adrenocorticotropic hormone.[113] There, however, is no convincing evidence of lowered cortisol levels in subjects where antipsychotics were used to manage depression.[114] It is still important to note that atypical antipsychotics have been shown to reduce cortisol levels, while typical antipsychotics do not have the same effect on the hypothalamic-pituitary-adrenal axis. In addition to this, typical antipsychotics have been shown to have limited effects on managing depressive symptoms.[115] Hence it can be deduced that the effects on cortisol levels may be partially responsible for the desired effects of antipsychotic therapy in depression, which therefore strengthens the understanding of the relationship between endocrinological pathways and the occurrence of depressive symptoms.

Finally, triiodothyronine augmentation in treatment-resistant depression has been discussed in literature and has been, to an extent, demonstrated to be an effective means of managing treatment-resistant depression. The definition of treatment resistance is, however, questionable in relation to these studies. Treatment-resistant depression, by definition, varies across literature. Mutual understanding among these sources is that at least two attempts with first-line treatment should have taken place, and adequate remission has not been achieved through these attempts. The subjects in earlier discussed studies had only undergone first-line treatment for depression, and there is no sufficient research to compare between other second-line treatment modalities for treatment-resistant depression. Despite this, the findings related to triiodothyronine augmentation therapy supported the efficacy of the therapy in patients who earlier have reached partial relief of symptoms with SSRIs or TCAs.

CONCLUSION

Major depressive disorder is one of the leading causes of disability worldwide, and hence a major public health concern. There exist a large array of pharmacological, neuromodulatory and psychological treatment options. Despite this, some patients do not find relief from typical antidepressant pharmacotherapy. Typically after two trials with first-line agents, the condition is declared treatment-resistant in its nature.

This literature review took a particular focus on the relationship between triiodothyronine, an active thyroid hormone, and serotonin receptors, particularly serotonin 1A-, 1B- and 2A-receptors. Triiodothyronine was found to have an effect on the concentration of serotonin autoreceptors. Serotonin autoreceptors are responsible for the downregulation of neuronal impulses through a negative feedback loop involving extracellular serotonin. With downregulation of serotonin 1A-, 1B- and 2A-receptors, the effects of antidepressants on postsynaptic serotonin receptors were found to be increased. Antidepressants' refractory treatment response was demonstrated to shorten in relation to triiodothyronine augmentation. Triiodothyronine augmentation is demonstrated to be most efficient in accelerating the effects of antidepressants.

The studies that provide evidence on the efficacy of adjunctive triiodothyronine therapy in depression are limited to subjects using selective-serotonin reuptake inhibitors or tricyclic antidepressants. Due to the research focusing around the change of millennium, the definition of treatment resistance is largely different from the current definition of treatment-resistant depression. Serotonin-noradrenaline receptors only gained their popularity in the 21st century, as Venlafaxine was only approved by the United States Food and Drug Administration in the mid- to late 1990's. Hence majority of the subjects in the biggest studies regarding the use of triiodothyronine in depression have only received either selective-serotonin reuptake inhibitors or tricyclic antidepressants prior to the adjunctive triiodothyronine therapy. In addition to this, a large portion of clinical studies are focused particularly on the use of tricyclic antidepressants. Although effective in managing depression, tricyclic antidepressants have lost their popularity after the introduction of serotonin-noradrenaline reuptake inhibitors, noradrenaline inhibitors, atypical antidepressants and serotonin modulators. As there is limited research regarding triiodothyronine augmentation in depression in the past 10 years, there also is no sufficient data to compare triiodothyronine augmentation with other choices of adjunctive therapy.

Triiodothyronine augmentation, as demonstrated by literature, is a relevant treatment option when considering patients who initially experienced some benefit from selective-serotonin reuptake inhibitors or tricyclic antidepressants, but quickly reached a plateau in their recovery. The major limitation of the research that is currently available is the lack of inclusion of other antidepressant groups. Overall, when comparing the evidence supporting the use of triiodothyronine augmentation with other adjunctive therapies, based on this

literature review it can be stated that triiodothyronine augmentation falls behind antipsychotic augmentation in terms of efficacy, treatment simplicity, and opportunities for individualization of care and safety. The demonstrated serotonin 1A-, 1B- and 2A-receptor activity is not unique to triiodothyronine, but can also be achieved with atypical antipsychotics, such as brexpiprazole and quetiapine. Unique feature of triiodothyronine augmentation, as compared to other modalities of adjunctive therapy, is its features as an accelerator of antidepressants. This may be applied in cases where rapid response to medication is required, such as in postpartum depression, or other depression with significant functional loss. Another factor supporting the use of triiodothyronine augmentation in comparison to other adjunctive therapies is the reported low incidence of adverse effects. In conclusion, triiodothyronine augmentation is an adjunctive therapy shown to be beneficial in accordance with the use of selective-serotonin reuptake inhibitors and tricyclic antidepressants, but in the larger spectrum it is outdated and has been replaced by more modern treatment approaches.

FURTHER RECOMMENDATIONS

There exists a lack of research regarding the use of triiodothyronine augmentation with other antidepressant groups apart from selective-serotonin reuptake inhibitors and tricyclic antidepressants. Research into the use of triiodothyronine augmentation with serotonin-noradrenaline reuptake inhibitors, atypical antidepressants and serotonin modulators could be beneficial to support the use of triiodothyronine augmentation in the future.

It could be beneficial to study the effects of triiodothyronine augmentation in the adolescent population, as selective-serotonin reuptake inhibitors are the only approved antidepressants for under 18-year-olds.

Research into comparing the effects of atypical antipsychotic adjunctive therapy and triiodothyronine augmentation with antidepressants would guide the clinical decision on which adjunctive therapy is more beneficial for a patient and would aid in individualizing treatment modality selection in treatment-resistant depression.

REFERENCES

1. National Collaborating Centre for Mental Health (UK). The classification of depression and depression rating scales/questionnaires [Internet]. U.S. National Library of Medicine; 1970 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK82926/

2. Tolentino JC, Schmidt SL. DSM-5 criteria and depression severity: Implications for clinical practice. Frontiers in Psychiatry. 2018 Oct 2;9. doi:10.3389/fpsyt.2018.00450

3. Conroy SK, Holtzheimer PE. Neuromodulation strategies for the treatment of depression. American Journal of Psychiatry. 2021 Dec;178(12):1082–8. doi:10.1176/appi.ajp.2021.21101034

4. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman‐Hoffman V, Green J, et al. Defining treatment‐resistant depression. Depression and Anxiety. 2019 Oct 22;37(2):134–45. doi:10.1002/da.22968

5. Chen P. Optimized treatment strategy for depressive disorder. Advances in Experimental Medicine and Biology. 2019;201–17. doi:10.1007/978-981-32-9271-0_11

6. Hensler JG, Artigas F, Bortolozzi A, Daws LC, De Deurwaerdère P, Milan L, et al. Catecholamine/serotonin interactions. A New Era of Catecholamines in the Laboratory and Clinic. 2013;167–97. doi:10.1016/b978-0-12-411512-5.00009-9

7. Voineskos D, Daskalakis ZJ, Blumberger DM. management of treatment-resistant depression: Challenges and strategies. Neuropsychiatric Disease and Treatment. 2020 Jan;Volume 16:221–34. doi:10.2147/ndt.s198774

8. Barchas JD. Monoamine hypotheses of mood disorders [Internet]. U.S. National Library of Medicine; 1999 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK28257/

9. Azizi SA. Monoamines: Dopamine, norepinephrine, and serotonin, beyond modulation, “switches” that alter the state of Target Networks. The Neuroscientist. 2020 Dec 9;28(2):121–43. doi:10.1177/1073858420974336

10. Shao X, Zhu G. Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder. Frontiers in Psychiatry. 2020 May 13;11. doi:10.3389/fpsyt.2020.00381

11. Jiang Y, Zou D, Li Y, Gu S, Dong J, Ma X, et al. Monoamine neurotransmitters control basic emotions and affect major depressive disorders. Pharmaceuticals. 2022 Sept 28;15(10):1203. doi:10.3390/ph15101203

12. Etchecopar-Etchart D, Korchia T, Loundou A, Llorca P-M, Auquier P, Lançon C, et al. Comorbid Major depressive disorder in schizophrenia: A systematic review and meta-analysis. Schizophrenia Bulletin. 2020 Nov 30;47(2):298–308. doi:10.1093/schbul/sbaa153

13. Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO. A corticosteroid/dopamine hypothesis for psychotic depression and related states. Journal of Psychiatric Research. 1985 Jan;19(1):57–64. doi:10.1016/0022-3956(85)90068-8

14. Duval F, Mokrani M-C, Crocq M-A, Bailey PE, Diep TS, Correa H, et al. Dopaminergic function and the cortisol response to dexamethasone in psychotic depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2000 Feb;24(2):207–25. doi:10.1016/s0278-5846(99)00098-6

15. Belujon P, Grace AA. Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology. 2017 Jun 29;20(12):1036–46. doi:10.1093/ijnp/pyx056

16. Rothe N, Steffen J, Penz M, Kirschbaum C, Walther A. Examination of peripheral basal and reactive cortisol levels in major depressive disorder and the Burnout Syndrome: A systematic review. Neuroscience & Biobehavioral Reviews. 2020 Jul;114:232–70. doi:10.1016/j.neubiorev.2020.02.024

17. Salvat-Pujol N, Labad J, Urretavizcaya M, de Arriba-Arnau A, Segalàs C, Real E, et al. Hypothalamic-pituitary-adrenal axis activity and cognition in major depression: The role of remission status. Psychoneuroendocrinology. 2017 Feb;76:38–48. doi:10.1016/j.psyneuen.2016.11.007

18. HS; J. Studies on the neuroendocrine role of serotonin [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/18208678/

19. Jørgensen H, Knigge U, Kjær A, Møller M, Warberg J. Serotonergic stimulation of corticotropin‐releasing hormone and pro‐opiomelanocortin gene expression. Journal of Neuroendocrinology. 2002 Oct;14(10):788–95. doi:10.1046/j.1365-2826.2002.00839.x

20. Asadikaram G, Khaleghi E, Sayadi A, Foulady S, Ghasemi MS, Abolhassani M, et al. Assessment of hormonal alterations in major depressive disorder: A clinical study. PsyCh Journal. 2019 May 20;8(4):423–30. doi:10.1002/pchj.290

21. Halaris A, Sohl E, Whitham EA. Treatment-resistant Depression revisited: A glimmer of HOPE. Journal of Personalized Medicine. 2021 Feb 23;11(2):155. doi:10.3390/jpm11020155

22. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: A Systematic Umbrella Review of the evidence. Molecular Psychiatry. 2022 Jul 20;28(8):3243–56. doi:10.1038/s41380-022-01661-0

23. Bamalan OA. Physiology, serotonin [Internet]. U.S. National Library of Medicine; 2023 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545168/

24. Bamalan OA. Physiology, serotonin [Internet]. U.S. National Library of Medicine; 2023 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545168/

25. Frazer A. Serotonin receptors [Internet]. U.S. National Library of Medicine; 1999 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK28234/

26. C; TMMR. Paroxetine and pindolol: A randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/9219043/

27. Artigas F, Celada P, Laruelle M, Adell A. How does pindolol improve antidepressant action? Trends in Pharmacological Sciences. 2001 May;22(5):224–8. doi:10.1016/s0165-6147(00)01682-5

28. Sahli ZT, Banerjee P, Tarazi FI. The preclinical and clinical effects of Vilazodone for the treatment of major depressive disorder. Expert Opinion on Drug Discovery. 2016 Mar 16;11(5):515–23. doi:10.1517/17460441.2016.1160051

29. Artigas F, Romero L, de Montigny C, Blier P. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends in Neurosciences. 1996 Jan;19(9):378–83. doi:10.1016/s0166-2236(96)10037-0

30. Siafis S, Tzachanis D, Samara M, Papazisis G. Antipsychotic drugs: From receptor-binding profiles to metabolic side effects. Current Neuropharmacology. 2018 Aug 21;16(8):1210–23. doi:10.2174/1570159x15666170630163616

31. Millan MJ, Lejeune F, Gobert A. Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: Relevance to the actions of antidepressant agents. Journal of Psychopharmacology. 2000 Mar;14(2):114–38. doi:10.1177/026988110001400202

32. Kennett GA, Dourish CT, Curzon G. Antidepressant-like action of 5-HT1A agonists and conventional antidepressants in an animal model of depression. European Journal of Pharmacology. 1987 Feb;134(3):265–74. doi:10.1016/0014-2999(87)90357-8

33. I; L. Behavioral studies of serotonin receptor agonists as antidepressant drugs [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/1684363/

34. Nautiyal KM, Hen R. Serotonin receptors in depression: From A to B. F1000Research. 2017 Feb 9;6:123. doi:10.12688/f1000research.9736.1

35. Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in Depression. Molecular Brain. 2017 Jun 24;10(1). doi:10.1186/s13041-017-0306-y

36. Armstrong M. Physiology, thyroid function [Internet]. U.S. National Library of Medicine; 2023 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537039/

37. Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. Physiological Reviews. 2014 Apr;94(2):355–82. doi:10.1152/physrev.00030.2013

38. Patil N. Hypothyroidism [Internet]. U.S. National Library of Medicine; 2023 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519536/

39. Joffe RT, Singer W. A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. Psychiatry Research. 1990 Jun;32(3):241–51. doi:10.1016/0165-1781(90)90029-5

40. Rosenthal LJ, Goldner WS, O'Reardon JP. T3 augmentation in major depressive disorder: Safety considerations. American Journal of Psychiatry. 2011 Oct;168(10):1035–40. doi:10.1176/appi.ajp.2011.10030402

41. Costache A;Riza AL;Popescu M;Dinca ME;Glavan DG;Vladu IM;Ioana M;Udristoiu I; TSH and T4 levels in a cohort of depressive patients [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/32874682/

42. Lekurwale V, Acharya S, Shukla S, Kumar S. Neuropsychiatric manifestations of thyroid diseases. Cureus. 2023 Jan 20; doi:10.7759/cureus.33987

43. Garlow SJ, Dunlop BW, Ninan PT, Nemeroff CB. The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. Journal of Psychiatric Research. 2012 Nov;46(11):1406–13. doi:10.1016/j.jpsychires.2012.08.009

44. Di Liegro I. Thyroid hormones and the central nervous system of mammals (review). Molecular Medicine Reports. 2008 May 1; doi:10.3892/mmr.1.3.279

45. Bocco BM, Werneck-de-Castro JP, Oliveira KC, Fernandes GW, Fonseca TL, Nascimento BP, et al. Type 2 deiodinase disruption in astrocytes results in anxiety-depressive-like behavior in male mice. Endocrinology. 2016 Aug 8;157(9):3682–95. doi:10.1210/en.2016-1272

46. Hage MP, Azar ST. The link between thyroid function and Depression. Journal of Thyroid Research. 2012;2012:1–8. doi:10.1155/2012/590648

47. Feng G, Kang C, Yuan J, Zhang Y, Wei Y, Xu L, et al. Neuroendocrine abnormalities associated with untreated first episode patients with major depressive disorder and bipolar disorder. Psychoneuroendocrinology. 2019 Sept;107:119–23. doi:10.1016/j.psyneuen.2019.05.013

48. Maglione AV, do Nascimento BP, Ribeiro MO, de Souza TJ, da Silva RE, Sato MA, et al. Triiodothyronine treatment reverses depression-like behavior in a triple-transgenic animal model of alzheimer's disease. Metabolic Brain Disease. 2022 Aug 11;37(8):2735–50. doi:10.1007/s11011-022-01055-9

49. Bauer M, Whybrow PC. Role of thyroid hormone therapy in Depressive Disorders. Journal of Endocrinological Investigation. 2021 Jun 15;44(11):2341–7. doi:10.1007/s40618-021-01600-w

50. Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus-pituitary-thyroid (hpt)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Molecular and Cellular Endocrinology. 2021 Apr;525:111173. doi:10.1016/j.mce.2021.111173

51. Hiller-Sturmhöfel S, Bartke A. The endocrine system: An overview [Internet]. U.S. National Library of Medicine; 1998 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6761896/

52. Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus-pituitary-thyroid (hpt)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Molecular and Cellular Endocrinology. 2021 Apr;525:111173. doi:10.1016/j.mce.2021.111173

53. Dwyer JB, Aftab A, Radhakrishnan R, Widge A, Rodriguez CI, Carpenter LL, et al. Hormonal treatments for major depressive disorder: State of the art. American Journal of Psychiatry. 2020 Aug 1;177(8):686–705. doi:10.1176/appi.ajp.2020.19080848

54. Gur E, Lifschytz T, Lerer B, Newman ME. Effects of triiodothyronine and imipramine on basal 5-HT levels and 5-HT1 autoreceptor activity in rat cortex. European Journal of Pharmacology. 2002 Dec;457(1):37–43. doi:10.1016/s0014-2999(02)02642-0

55. Nautiyal KM, Tritschler L, Ahmari SE, David DJ, Gardier AM, Hen R. A lack of serotonin 1B autoreceptors results in decreased anxiety and depression-related behaviors. Neuropsychopharmacology. 2016 Jun 29;41(12):2941–50. doi:10.1038/npp.2016.109

56. Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: Rationale and current status of research. CNS Drugs. 2013 Jun 12;27(9):703–16. doi:10.1007/s40263-013-0071-0

57. Diez D, Grijota-Martinez C, Agretti P, De Marco G, Tonacchera M, Pinchera A, et al. Thyroid hormone action in the adult brain: Gene expression profiling of the effects of single and multiple doses of Triiodo-l-thyronine in the rat striatum. Endocrinology. 2008 May 8;149(8):3989–4000. doi:10.1210/en.2008-0350

58. Lifschytz T, Goltser-Dubner T, Landshut G, Lerer B. Effect of triiodothyronine on 5-HT1A and 5-HT1B receptor expression in rat forebrain and on latency to feed in the novelty suppressed feeding

test. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2010 May;34(4):632–8. doi:10.1016/j.pnpbp.2010.02.029

59. Yin L, Zhang Y, Zhang X, Yu T, He G, Sun X. TPH, SLC6A2, SLC6A3, DRD2 and DRD4 polymorphisms and neuroendocrine factors predict ssris treatment outcome in the Chinese population with major depression. Pharmacopsychiatry. 2015 Feb 2;48(03):95–103. doi:10.1055/s-0034-1398508

60. Bockaert J, Claeysen S, Bécamel C, Dumuis A, Marin P. Neuronal 5-HT metabotropic receptors: Fine-tuning of their structure, signaling, and roles in synaptic modulation. Cell and Tissue Research. 2006 Aug 1;326(2):553–72. doi:10.1007/s00441-006-0286-1

61. Riad M;Garcia S;Watkins KC;Jodoin N;Doucet E;Langlois X;el Mestikawy S;Hamon M;Descarries L; SOMATODENDRITIC localization of 5-HT1A and preterminal axonal localization of 5-HT1B serotonin receptors in adult rat brain [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/10660896/

62. Niebert S, van Belle GJ, Vogelgesang S, Manzke T, Niebert M. The serotonin receptor subtype 5B specifically interacts with serotonin receptor subtype 1A. Frontiers in Molecular Neuroscience. 2017 Sept 21;10. doi:10.3389/fnmol.2017.00299

63. BLIER P, PIÑEYRO G, EL MANSARI M, BERGERON R, DE MONTIGNY C. Role of somatodendritic 5‐HT autoreceptors in modulating 5‐HT neurotransmission. Annals of the New York Academy of Sciences. 1998 Dec;861(1):204–16. doi:10.1111/j.1749-6632.1998.tb10192.x

64. Celada P, Puig M, Amargós-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT1A and 5-HT2A receptors in Depression [Internet]. U.S. National Library of Medicine; 2004 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC446220/

65. Sandrini M, Vitale G, Vergoni AV, Ottani A, Bertolini A. Effect of acute and chronic treatment with triiodothyronine on serotonin levels and serotonergic receptor subtypes in The rat brain. Life Sciences. 1996 Mar;58(18):1551–9. doi:10.1016/0024-3205(96)00129-4

66. Moreau X. Chronic effects of triiodothyronine in combination with imipramine on 5-HT transporter, 5-HT1A and 5-HT2A receptors in adult Rat Brain. Neuropsychopharmacology. 2001 Jun;24(6):652–62. doi:10.1016/s0893-133x(00)00234-7

67. Lee J-H, Lee M, Park J-A, Ryu YH, Lee KC, Kim KM, et al. Effects of hypothyroidism on serotonin 1A receptors in The rat brain. Psychopharmacology. 2017 Dec 5;235(3):729–36. doi:10.1007/s00213-017-4799-y

68. Segerson TP, Kauer J, Wolfe HC, Mobtaker H, Wu P, Jackson IM, et al. Thyroid hormone regulates trh biosynthesis in the paraventricular nucleus of the rat hypothalamus. Science. 1987 Oct 2;238(4823):78–80. doi:10.1126/science.3116669

69. Touma KTB, Zoucha AM, Scarff JR. Liothyronine for Depression: A review and guidance for Safety Monitoring [Internet]. U.S. National Library of Medicine; 2017 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5451035/

70. Lifschytz T, Segman R, Shalom G, Lerer B, Gur E, Golzer T, et al. Basic mechanisms of augmentation of antidepressant effects with thyroid hormone. Current Drug Targets. 2006 Feb 1;7(2):203–10. doi:10.2174/138945006775515482

71. PRANGE AJ, WILSON IC, RABON AM, LIPTON MA. Enhancement of imipramine antidepressant activity by thyroid hormone. American Journal of Psychiatry. 1969 Oct;126(4):457–69. doi:10.1176/ajp.126.4.457

72. Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. American Journal of Psychiatry. 2001 Oct;158(10):1617–22. doi:10.1176/appi.ajp.158.10.1617

73. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient clinic: Clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. The International Journal of Neuropsychopharmacology. 2003 Mar;6(1):41–9. doi:10.1017/s146114570200322x

74. Cooper-Kazaz R, Apter JT, Cohen R, Karagichev L, Muhammed-Moussa S, Grupper D, et al. Combined treatment with sertraline and liothyronine in major depression. Archives of General Psychiatry. 2007 Jun 1;64(6):679. doi:10.1001/archpsyc.64.6.679

75. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. The International Journal of Neuropsychopharmacology. 2007 Nov 30;11(05). doi:10.1017/s1461145707008206

76. Appelhof BC, Brouwer JP, van Dyck R, Fliers E, Hoogendijk WJ, Huyser J, et al. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. The Journal of Clinical Endocrinology & Metabolism. 2004 Dec;89(12):6271–6. doi:10.1210/jc.2004-1147

77. Dale E, Bang-Andersen B, Sánchez C. Emerging mechanisms and treatments for depression beyond ssris and snris. Biochemical Pharmacology. 2015 May;95(2):81–97. doi:10.1016/j.bcp.2015.03.011

78. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, et al. A comparison of lithium and T3augmentation following two failed medication treatments for depression: A star*d report. American Journal of Psychiatry. 2006 Sept;163(9):1519–30. doi:10.1176/ajp.2006.163.9.1519

79. Homan P, Drevets WC, Hasler G. Neural correlates of free T3 alteration after catecholamine depletion in subjects with remitted major depressive disorder and in controls. Psychopharmacology. 2013 Aug 18;231(2):409–17. doi:10.1007/s00213-013-3250-2

80. Gur E, Lifschytz T, Van de Kar LD, Lerer B, Newman ME. Effects of triiodothyronine on 5-HT1A and 5-HT1B autoreceptor activity, and postsynaptic 5-HT1A receptor activity, in rat hypothalamus: Lack of interaction with imipramine. Psychoneuroendocrinology. 2004 Oct;29(9):1172–83. doi:10.1016/j.psyneuen.2004.01.011

81. Gur E, Lifschytz T, Lerer B, Newman ME. Effects of triiodothyronine and imipramine on basal 5-HT levels and 5-HT1 autoreceptor activity in rat cortex. European Journal of Pharmacology. 2002 Dec;457(1):37–43. doi:10.1016/s0014-2999(02)02642-0

82. Best J, Duncan W, Sadre-Marandi F, Hashemi P, Nijhout HF, Reed M. Autoreceptor control of serotonin dynamics. BMC Neuroscience. 2020 Sept 23;21(1). doi:10.1186/s12868-020-00587-z

83. Nautiyal KM, Tritschler L, Ahmari SE, David DJ, Gardier AM, Hen R. A lack of serotonin 1B autoreceptors results in decreased anxiety and depression-related behaviors. Neuropsychopharmacology. 2016 Jun 29;41(12):2941–50. doi:10.1038/npp.2016.109

84. Hagan CE, Mcdevitt RA, Liu Y, Furay AR, Neumaier JF. 5‐HT1B autoreceptor regulation of serotonin transporter activity in synaptosomes. Synapse. 2012 Sept 29;66(12):1024–34. doi:10.1002/syn.21608

85. Moreau X, Azorin J-M, Lejeune P-J, Jeanningros R. Red Blood Cell triiodothyronine uptake in unipolar major depression: Effect of a chronic antidepressant treatment. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2000 Jan;24(1):23–35. doi:10.1016/s0278-5846(99)00087-1

86. Richardson-Jones JW, Craige CP, Guiard BP, Stephen A, Metzger KL, Kung HF, et al. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron. 2010 Jan;65(1):40–52. doi:10.1016/j.neuron.2009.12.003

87. Wheatley D. Potentiation of amitriptyline by thyroid hormone. Archives of General Psychiatry. 1972 Mar 1;26(3):229. doi:10.1001/archpsyc.1972.01750210037008

88. Joffe RT. Hormone treatment of depression. Dialogues in Clinical Neuroscience. 2011 Mar 31;13(1):127–38. doi:10.31887/dcns.2011.13.1/rjoffe

89. Aronson R. Triiodothyronine augmentation in the treatment of refractory depression. Archives of General Psychiatry. 1996 Sept 1;53(9):842. doi:10.1001/archpsyc.1996.01830090090013

90. Bhella VS, Garg D. Use of liothyronine (L-T3) as an augmentation therapy for depression during pregnancy. BMJ Case Reports. 2018 Dec;11(1). doi:10.1136/bcr-2018-225852

91. Moret C. Combination/augmentation strategies for improving the treatment of depression [Internet]. U.S. National Library of Medicine; 2005 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2424118/

92. Cohrs S, Röher C, Jordan W, Meier A, Huether G, Wuttke W, et al. The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. Psychopharmacology. 2006 Jan 24;185(1):11–8. doi:10.1007/s00213-005-0279-x

93. Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. Journal of Affective Disorders. 2006 Apr;91(2–3):211–5. doi:10.1016/j.jad.2006.01.013

94. Schüle C, Baghai ThC, Alajbegovic L, Schwarz M, Zwanzger P, Eser D, et al. The influence of 4–week treatment with sertraline on the combined T3/TRH test in depressed patients. European Archives of Psychiatry and Clinical Neuroscience. 2005 Mar 5;255(5):334–40. doi:10.1007/s00406-005-0571-0

95. Gitlin M;Altshuler LL;Frye MA;Suri R;Huynh EL;Fairbanks L;Bauer M;Korenman S; Peripheral thyroid hormones and response to selective serotonin reuptake inhibitors [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/15486607/

96. de Carvalho GA, Bahls S-C, Boeving A, Graf H. Effects of selective serotonin reuptake inhibitors on thyroid function in depressed patients with primary hypothyroidism or normal thyroid function. Thyroid. 2009 Jul;19(7):691–7. doi:10.1089/thy.2008.0261

97. Gitlin M. Failure of T3 to potentiate tricyclic antidepressant response. Journal of Affective Disorders. 1987 Dec;13(3):267–72. doi:10.1016/0165-0327(87)90046-2

98. Bschor T. Lithium in the treatment of major depressive disorder. Drugs. 2014 May 14;74(8):855–62. doi:10.1007/s40265-014-0220-x

99. McKnight RF, de La Motte de Broöns de Vauvert SJGN, Chesney E, Amit BH, Geddes J, Cipriani A. Lithium for acute mania. Cochrane Database of Systematic Reviews. 2019 Jun 1;2019(6). doi:10.1002/14651858.cd004048.pub4

100. Young AH, Hammond JM. Lithium in mood disorders: Increasing evidence base, declining use? British Journal of Psychiatry. 2007 Dec;191(6):474–6. doi:10.1192/bjp.bp.107.043133

101. Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. Clinical Practice and Epidemiology in Mental Health. 2006;2(1):23. doi:10.1186/1745-0179-2-23

102. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. International Journal of Bipolar Disorders. 2015 Jun 5;3(1). doi:10.1186/s40345-015-0028-y

103. Bauer M, Whybrow PC. Thyroid hormone, neural tissue and mood modulation. The World Journal of Biological Psychiatry. 2001 Jan;2(2):59–69. doi:10.3109/15622970109027495

104. Mikulska J, Juszczyk G, Gawrońska-Grzywacz M, Herbet M. HPA axis in the Pathomechanism of depression and schizophrenia: New therapeutic strategies based on its participation. Brain Sciences. 2021 Sept 30;11(10):1298. doi:10.3390/brainsci11101298

105. BUNNEY WE. Norepinephrine in depressive reactions. Archives of General Psychiatry. 1965 Dec 1;13(6):483. doi:10.1001/archpsyc.1965.01730060001001

106. Walshaw PD;Gyulai L;Bauer M;Bauer MS;Calimlim B;Sugar CA;Whybrow PC; Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: A double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3) [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/29869405/

107. Jennifer L Galjour M. Lithium level [Internet]. Medscape; 2022 [cited 2024 Apr 25]. Available from: https://emedicine.medscape.com/article/2090174-overview?form=fpf

108. Gambi F;De Berardis D;Sepede G;Campanella D;Galliani N;Carano A;La Rovere L;Salini G;Penna L;Cicconetti A;Spinella S;Quartesan R;Salerno RM;Ferro FM; Effect of mirtazapine on thyroid hormones in adult patients with major depression [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/16388723/

109. Dalan R, Leow MK, Jong M. Multiple endocrinopathies associated with lithium therapy. Endocrine Practice. 2007 Nov;13(7):758–63. doi:10.4158/ep.13.7.758

110. Joffe RT. How should lithium-induced thyroid dysfunction be managed in patients with bipolar disorder? [Internet]. U.S. National Library of Medicine; 2002 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC161685/

111. Han C;Wang SM;Kato M;Lee SJ;Patkar AA;Masand PS;Pae CU; Second-generation antipsychotics in the treatment of major depressive disorder: Current evidence [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/23898855/

112. Wang S-M, Han C, Lee S-J, Jun T-Y, Patkar AA, Masand PS, et al. Second generation antipsychotics in the treatment of major depressive disorder: An update [Internet]. U.S. National Library of Medicine; 2016 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5040765/

113. Taneja C;Papakostas GI;Jing Y;Baker RA;Forbes RA;Oster G; Cost-effectiveness of adjunctive therapy with atypical antipsychotics for acute treatment of major depressive disorder [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/22550279/

114. Daly EJ, Trivedi MH. A review of Quetiapine in combination with antidepressant therapy in patients with depression [Internet]. U.S. National Library of Medicine; 2007 [cited 2024 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656328/

115. Sagud M;Mihaljević-Peleš A;Begić D;Vuksan-Ćusa B;Kramarić M;Zivković M;Jakovljević M; Antipsychotics as antidepressants: What is the mechanism? [Internet]. U.S. National Library of Medicine; [cited 2024 Apr 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/21963702/

ANNEXES

Annex 1:

Table 1.

Selection criteria	Key words: Thyroid, depression, T3, triiodothyronine	Type of study: clinical trial, meta-analysis, randomized controlled trial	Year of publication: no selection was made due to low quantity of recent research	Rejected due to methodological inadequacies	Relevant: studies relevant to the scope of this review, that meet the inclusion criteria
Number of studies	593	52	52	1	17

Literature selection criteria on most relevant studies according to PubMed search engine.

Annex 2:

Table 2.

Reference number	Study	Authors	Year of publication	Type of study	Main outcome
39	A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants	Joffe R., Singer W.	1990	Clinical trial	Statistically significant decrease in depressive symptoms in subjects treated with T3 in comparison to subjects on T4.
43	The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in	Garlow S., Dunlop B., Ninan P., Nemeroff C.	2012	Randomized controlled trial	There was no statistically significant difference between placebo and T3 treated

	the treatment of major depressive disorder				subjects.
59	TPH, SLC6A2, SLC6A3, DRD2 and DRD4 Polymorphisms and Neuroendocrine Factors Predict SSRIs Treatment Outcome in the Chinese Population with Major Depression	Yin L., Zhang Y., Zhang X., Yu T., He G., Sun X.	2015	Randomized controlled trial	There is statistically significant difference in SSRI response comparing between different genotypes due to DRD4 gene polymorphism.
72	Does Thyroid Supplementation Accelerate Tricyclic Antidepressant Response? A Review and Meta-Analysis of the Literature	Altshuler L., Bauer M., Frye M., Gitlin M., Mintz J., Szuba M., Leight K., Whybrow P.	2001	Meta-analysis	Adjunctive T3 accelerated the response to TCAs.
73	Algorithm-based treatment of major depression in an outpatient clinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation	Agid O., Lerer B.	2003	Case-control study	T3 is effective in patients who do not respond initially to SSRIs. Women have a better outcome with T3. Subjects who were responsive to T3 had higher TSH levels (within range) prior to treatment.
74	Combined Treatment With Sertraline and Liothyronine in Major Depression A Randomized, Double-blind, Placebo-Controlle d Trial	Cooper- Kazaz R., Apter J., Cohen R.	2007	Randomized controlled trial	Effects of sertraline were enhanced without a significant increase of adverse effects when combined with T3.
75	Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake	Cooper- Kazaz R., Lerer B.	2008	Meta-analysis	Inconclusive findings in terms of efficacy. No increase in adverse effects when combining T3 with SSRIs.

	inhibitors				
76	Triiodothyronine Addition to Paroxetine in the Treatment of Major Depressive Disorder	Appelhof B., Brouwer J., van Dyck R., Fliers E., Hoogendijk W., Huyser J., Schene A., Tijssen J., Wiersinga W.	2004	Randomized controlled trial	T3 augmentation with SSRI Paroxetine did not show an accelerated effect in men nor women. More adverse effects occurred on T3 augmentation.
79	Neural correlates of free T3 alteration after catecholamine depletion in subjects with remitted major depressive disorder and in controls	Homan P., Drevets W., Hasler G.	2013	Randomized controlled trial	T3 and T4 levels were less suppressed after catecholamine depletion. Positive association between T3 and T4 and depressive symptoms.
85	Red blood cell triiodothyronine uptake in unipolar major depression: effect of a chronic antidepressant treatment	Moreau X., Azorin J., Lejejune P., Jeanningros R.	2000	Clinical trial	T3 uptake by red blood cells was found to be higher in depressed subjects than in healthy individuals. After 4 weeks of treatment with fluvoxamine, T3 uptake was lowered when compared to baseline, in responsive subjects.
87	Failure of T3 to potentiate tricyclic antidepressant response	Gitlin M., Weiner H., Fairbanks, Hershman J., Friedfeld N.	1987	Clinical trial	There was no statistically significant correlation between imipramine nonresponders treated with T3 and improvement of depressive symptoms.
93	T3 augmentation of SSRI resistant depression	Abraham G., Milev R., Lawson J.	2006	Clinical trial	There was a statistically significant decrease in depressive symptoms in

					patients treated with T3 alongside SSRIs.
94	Peripheral thyroid hormones and response to selective serotonin reuptake inhibitors	Gitlin M., Altschuler L., Frye M., Suri R., Huynh E., Fairbanks L., Bauer M., Korenman S.	2004	Clinical trial	Low TSH values showed statistically significant correlation in improvement of depressive symptoms when treated with SSRIs.
96	Effects of selective serotonin reuptake inhibitors on thyroid function in depressed patients with primary hypothyroidism or normal thyroid function	De Carvalho G., Bahls S-C., Boeving A., Graf H.	2009	Randomized controlled trial	There were no statistically significant changes in thyroid function with the use of fluoxetine or sertraline on euthyroid or hypothyroid subjects. Euthyroid subjects were found to be more susceptible to minor changes in the serotonergic system than hypothyroid subjects.
106	Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: A double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3)	Walshaw P., Gyulai L., Bauer M., Bauer M.S., Calimlim B., Sugar C., Whybrow P.	2018	Randomized controlled trial	Adjunctive T4 therapy showed statistically significant improvement in treatment-resistant bipolar disorder, while T3 augmentation did not demonstrate statistically significant improvement compared to placebo.
108	Effect of mirtazapine on thyroid hormones in adult patients with major depression	Gambi F., De Berardis D., Sepede G., Campanella D., Galliani N., Carano A., La Rovere L., Salini G.,	2005	Clinical trial	Higher T3 levels were present after 6-month use of mirtazapine, while lower T4 levels were present, compared to baseline.

		Penna L., Cicconetti A., Spinella S., Quartesan R., Salerno R., Ferro F.			Higher T3 levels correlated with lesser depressive symptoms, and higher T4 levels correlated with higher depressive symptoms at the end of the treatment.
116	The influence of 4-week treatment with sertraline on the combined T3/TRH test in depressed patients	Schüle C., Baghai T., Alajbegovic L., Schwarz M., Zwanzger P., Eser D., Schaaf L. Möller H-J., Rupprecht R.	2005	Clinical trial	There was no statistically relevant correlation found between sertraline therapy and pituitary gland stimulation.

Summarized information on most relevant studies