THE WORKINGS AND PARADOXICAL EFFECTS OF ANTIDEPRESSANT MEDICATION

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Carina A. A. Schoenmaker
S2498529
Bachelor's thesis for Neurowetenschappen research
University of Groningen
9747 AG Groningen
c.a.a.schoenmaker@student.rug.nl

Supervisor: Prof. dr. Ulrich L. M. Eisel
University of Groningen
9747 AG Groningen
u.l.m.eisel@rug.nl

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ABSTRACT

Patients with Major Depressive Disorder are often treated using antidepressant medication such as Selective Serotonin Reuptake Inhibitors or Tricyclic Antidepressants. Some studies have been published that show that these antidepressants may deteriorate the state of the depression and even cause suicidal ideation or action. This literature review gives an overview of the aetiology of MDD, as far as this has been uncovered. A short overview of medications and alternative treatments available is described. This raises the question which mechanics are behind the paradoxical workings of antidepressant medication. The main hypothesis says that when serotonergic pathways are altered due to administration of elective Serotonin Reuptake Inhibitors or Tricyclic Antidepressants, not only serotonin but also glutamate levels are affected. An increase of serotonin, causing the patient to be more activated, and a decrease of glutamate, resulting in a decrease in mood. Another hypothesis discusses the difference between individuals in vulnerability to depression and antidepressants, causing an unexpected effect in response to medication in a patient.

1 Introduction

In 2015 an enormous number of 322 million people (4.4 %) in the world lived with depression. For a considerable portion of this group, it is unbearable to live with this disease, which may result in a suicide attempt. Suicide has accounted for 1.5 % of all deaths worldwide in this year, which puts it in the top 20. (World Health Organization, 2017) Not all these suicides are necessarily caused by depression. However, even without thoughts or attempts at suicide, depression causes an enormous burden on our society. Symptoms cause pressure on a patient's life as well as on their surroundings. Estimations for the United States showed that absence from work and suboptimal performance due to depression cost $36.6 billion dollars in 2011 (Lépine & Briley, 2011). This accounts for 1.5% of the total federal budget of 2.3 trillion dollars (U.S. Office of Management and Budget, 2010). So far beneficial effects of antidepressants have been shown , however, symptoms are improved in 20-30 % of all patients which is not nearly enough (Bridge et al., 2007)(InformedHealth.org, 2017). Currently there is little understanding of the neurobiological and external factors contributing to a depression. In order to decrease the risk of suicide, it is essential to start to understand the disease better in order to provide better health care.

In general it is assumed that antidepressants provide a mostly beneficial solution to treat depression. However, Wirshing et al. (1992) report five cases of women who experience worsening depressive symptoms as a result of fluoxetine prescription. Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) that is said to have an antidepressant effect through enhancing serotonin pathways (Benfield et al., 1986). But in these five women, fluoxetine effects seem to be paradoxical and their depression deteriorates. After a few days of taking fluoxetine they reported many severe symptoms among which were suicidal thoughts. These symptoms disappeared within days after discontinuation with the antidepressant. More studies have been published that report results in which different antidepressant medications

seem do induce suicidal ideation or suicide attempts (Sharma et al., 2016) (Jureidini et al., 2004)(Whitehead, 2003). Since there is a poor understanding of depression overall, there is no clear theory about the cause of these contradictory effects.

In this report, hypotheses will be explored in this regard. First, an overview of current processes that are connected to depression will be given. Secondly, a description of available antidepressant treatments will be presented. Then, some possible mechanisms behind the paradoxical effect of antidepressants will be discussed. A discussion on the relevant research will be held, giving some implications for the future. A few recommendations on how to deal with paradoxical effects of antidepressant treatments will be mentioned.

2 What is depression?

Major Depressive Disorder (MDD), commonly known as depression, is a psychiatric disease with symptoms that can occur over long, sometimes interrupted periods of time. Important associated symptoms are depressed mood, loss of pleasure, feelings of guilt, suicidal ideation and intent, insomnia, loss of energy and fatigue. The symptoms have to be present for at least 2 weeks. (Fröhlich, 2016) However, these symptoms differ greatly per individual and may even be contradictory, as for example insomnia or hypersomnia might both occur in MDD.

Because of the lack of clarity in underlying mechanisms behind a depression, it is difficult to diagnose and classify the different types based solely on aetiology. An often used system is the Diagnostic and Statistical Manual of Mental Diseases (DSM). Several revised versions have been published for this system. The DSM-IV bases types of MDD on duration, severity and specific pattern of the symptoms. Specific types described are psychotic depression, melancholia, atypical features, catatonia, seasonal affective disorder and post-partum onset. (National Collaborating Centre for Mental Health (UK), 2010) Other common depressive disorders are bipolar, depression which is also known as manic depression, anxious depression, early or late onset depression and treatment resistant depression (Baumeister & Parker, 2012). Within the described subtypes, overlap can occur and moreover, subtypes rarely appear in pure form. This makes diagnosing difficult and a greater understanding of the fundamentals of MDD will help with classification and more directed care.

Although there is a consensus about certain psychological and biological mechanisms and consequences of MDD, a full explanation behind the causes of the disease is unfinished (Palazidou, 2012). Most knowledge available about the mechanisms behind depression comes from antidepressant medication action (Artigas et al., 2002). The structural and chemical changes that can be observed in patients suffering from depression will be described in this chapter.

2.1 Anatomical abnormalities observed in Major Depressive Disorder

In depressed patients a decrease of brain volume has been found in the prefrontal cortex (PFC), the amygdala and the hippocampus. An important function of the PFC is regulating complex cognitive behavior and emotions using sensorimotor information. The amygdala plays a role in cortical arousal, emotional learning and memory after unexpected stimuli. The hippocampus is an important brain structure involved in memory and learning processes, it is closely linked to the hypothalamo-pituitary-adrenal axis (HPA, see 2.3) and is important for neo-neurogenesis; thus synaptic plasticity.

By use of Positron Emission Tomography scan, abnormalities were discovered in the PFC of depressed patients in regional cerebral blood flow and glucose metabolism. An increase in metabolism was found in the ventromedial PFC and in the orbital PFC, a decrease in the dorsolateral PFC. A reduction in neuronal and glial density was measured in the PFC. The ventromedial PFC is involved in the generation of emotions, autonomic and neuroendocrine responses, pain modulation, aggression and sexual behaviour. The orbital PFC together with the amygdala corrects behaviour and emotional responses. The dorsolateral PFC is important for cognitive control, solving complex tasks, maintenance and manipulation of information in the working memory. Decreased activity of the PFC causes a impairment in the inhibition of limbic structures. Consequences are highly activated limbic structures, this disturbance is thought to be one of the causes of MDD.

Abnormal activity in the amygdala and severeness of depression have been linked, specifically in anxiety and bipolar depression. There is no strong evidence for specific changes in amygdala volume. Decrease in brain volume in the hippocampus was only visible in patients who had multiple depressive episodes. High risk groups for depression were also found to have a smaller hippocampus. These two findings together suggest that such abnormalities in the hippocampus lead to a high risk of depression. In the white matter of the brain hyperintensities and abnormalities are found in the micro-structure in the cortical-subcortical neuronal circuit, related to the seriousness of MDD. This has also been thought to play an important role in the pathophysiology of depression. (Palazidou, 2012)

2.2 Neurochemistry

Most antidepressant medication works by altering neurochemical pathways (see 3.1, which has proven important insights in how these mechanisms work. Serotonin has appeared to be the most important substance in the system for the past few decades. Serotonin is a monoamine, as well as noradrenalin and dopamine. The monoamine hypothesis states that the main cause of depression is a low concentration of monoamines (neurotransmitters with a specific molecular structure) in the cerebrospinal fluid of the central nervous system, potentially caused by high levels of the enzyme monoamine oxidase-A (Waller & Sampson, 2017). The workings of this enzyme will be further explained in chapter 3.1.2. The two relevant monoamines for depression are serotonin and noradrenaline. Serotonergic and noradrenergic systems in the central nervous system are closely connected. The locus coeruloeus and the dorsal and median raphe nuclei in the brainstem are the main sources of noradrenaline and serotonin, respectively. These signaling systems are closely linked; both activate most of the forebrain and the same intracellular signalling pathways. (Duman et al., 1999) A depletion of monoamines results in an impairment in excitatory signaling, causing understimulation of regions of the brain involved in emotional, cognitive and learning behaviour. Therefore, low monoamine values in an individual may result to give them a depressed feeling. (Palazidou, 2012)

Next to serotonin and noradrenaline, glutamatergic neurotransmission plays a vital role in the development of depressive disorders. Glutamate pathways are found to be linked to behaviour related to positively associated learning, pleasure and hedonism (Liu et al., 2014). Glutamate vesicles are located in serotonergic neurons in the raphe nuclei in the brainstem (El Mestikawy et al., 2011), this suggest glutamate excretion is stimulated in a similar manner as serotonin.

Another important depression related substance in the brain is Brain-Derived Neurotrophic Factor (BDNF). BDNF is released by the hippocampus, its main purposes entail neuronal growth, survival and maturation of neurons with synaptic plasticity as a result. BDNF and other neurotrophic growth factors such as vascular endothelial growth factor, fibroblast growth factor 2, insulin-like growth factor 1 play a part in depression. (Duman et al., 2016) In stress as well as depression the synthesis of BDNF is counteracted and in patients with untreated depression BDNF concentrations in the hippocampus and PFC are lower than in treated patients or untreated, healthy people (Palazidou, 2012).

2.3 Stress

The hypothalamic-pituitary-adrenal axis (HPA) is a neuroendocrine mechanism which plays a major role during the stress response in regulation of metabolism and immunological and neuronal activity. The hypothalamus secretes corticotropin-releasing factor (CRF) and vasopressin (ADH), which activate the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortex to secrete glucocorticoids (cortisol in humans). A negative-feedback balance between glucocorticoids and the secretion of CRF, ADH and ACTH exists. In depression, impaired glucocorticoid and mineralocorticoid receptor expression cause a reduce in feedback inhibition. As a result, elevated levels of cortisol and an increase in size of adrenal and pituitary glands can be measured. The disturbance in the feedback mechanisms causes an impairment in the regulation of stress in depression. (Pariante & Lightman, 2008)

2.4 Immunology

Immunological processes have also been proven play a role in the development of depression. Increased proinflammatory cytokines in an activated immune system are found in patients with depressive symptoms. This increase is associated with changes in noradrenergic activity and a decrease of tryptophan, a precursor for serotonin, and stimulated HPA axis (see 2.3). An increase in cytokines may therefore cause an impairment of glucocorticoid receptor function. Glucocorticoid resistance has further inflammation as an effect. The impairments of glucocorticoid receptors and chronically elevated proinflammatory cytokines have been associated with stress and chronic physical illness. This association may explain high risk for chronic illness in depressed patients. (Palazidou, 2012)

2.5 Genetics

Genes associated with depression and suicidal ideation might help with risk prediction or more specifically targeted treatment. The factors that may influence depression mechanisms described before are monoamine and other neurotransmitter pathways, brain structure, synaptic plasticity, neuroendocrine substances or neuroinflammation. All have a genetic basis. A few important genes have been uncovered to have an association to depression. Firstly, the 5-HTTLPR region is a promotor region encoding for the serotonin transporter. An association has been found between this region and bipolar disorder and suicidality (Galili-Weisstub & Segman, 2010). Gene-environment interactions appear important, also with 5-HTTLPR. People that carry the short allele for this gene and have endured stressful events in their life were more susceptible to depression (Caspi et al., 2003) and monoamine oxidase A (MAO, see 3.1.2) may moderate the effects of the gene (Cicchetti et al., 2007). Another mechanism that has a genetic basis that has been

examined are BDNF variations that influence brain structure. Carriers of the met-allele, that had methionine instead of valine in BDNF prion proteins, showed decreases in hippocampal volume, in healthy ánd depressed patients. Lower volumes were independent of age and the reduction of volume continues with age in subjects with the met-BDNF gene. A decreased hippocampus in combination with stress, this causes a vulnerability to develop depression (Frodl et al., 2008).

In summary, the described processes have overlap and influence each other greatly. Genetic basis for all described mechanisms has to be explored further in a chance to reveal important disease predictors or treatment possibilities. However many treatments already exist, they are described in the next chapter, there is much room for improvement.

3 Treatments

Even though the understanding of the mechanisms behind MDD is not complete, there are multiple relatively effective treatments, differing from medication, behavioral therapy, sleep deprivation to electrotherapy. Often it takes a few of these options or combinations of them to find a suitable treatment for the patient, which may take a few months. Antidepressant medication is effective in about 20-30% of all patients, varying from what type of medication is used (InformedHealth.org, 2017). Much prescribed antidepressants since the 1950s have been Tricyclic Antidepressants (TCA) and Monoamine Oxidase Inhibitors (MAOIs). In the 90s SSRIs took over. The increase of levels of serotonin and norepinephrine in the synaptic cleft is the main antidepressant function of these medications and others described in this chapter. This course of action confirms the monoamine hypothesis, which is part of the solution of the mechanism behind depression. (Artigas et al., 2002) Although the outcome in increasing monoamine levels is similar, there is no simple mechanism description for all types of antidepressants. Three general paths are used: monoamine reuptake inhibition, receptor blockade and inhibition of monoamine degrading enzymes (most importantly monoamine oxidase) (Duman et al., 1999).

3.1 Workings of antidepressant medication

3.1.1 Neurotransmitter (monoamine) reuptake inhibition

Selective Serotonin Reuptake Inhibitors As the name suggests, SSRIs use a method of inhibiting the reuptake of serotonin. This is done by competitive inhibition of the serotonin transporter (SERT). These transporters are proteins that transport serotonin back to be stored in the presynaptic neuron after a firing, cutting of its action in the synapse. By inhibiting the reuptake of serotonin by transporter proteins, an increase in serotonin in the synaptic cleft and a decrease in intracellular serotonin take place. This effect may take place within minutes or hours after taking SSRI medication. (Artigas et al., 2002)

The 5-HT$_1a$ receptor plays an important role in generation of action potentials in serotonergic neurons. When serotonin levels increase, through a negative feedback mechanism, 5-HT$_1a$ receptors are inhibited and firing rates decrease. The decrease of this rate depends on the dose of the medication. (Gartside et al., 1995) Although serotonin release decreases through 5-HT$_1a$ receptor inhibition, serotonin levels appear to stay elevated after SSRI administration (Marek et al., 2005).

Furthermore, SSRI has been found to play a role in the increase of BDNF expression and thereby block deficits in growth factor expression that may be caused by stress and depression (Duman et al., 2016).

SSRIs have low antagonistic affinity for postsynaptic muscarinic/α_1-adreno/histamine receptors, which gives this type of drugs the advantage of having fewer side effects than many other antidepressant drugs. (Waller & Sampson, 2017) SSRIs are the most prescribed antidepressant, with citalopram, fluvoxamine, paroxetine, fluoxetine and sertraline as the five main SSRIs (Kauffman, 2009). A considerable amount of research is attributed to SSRI workings, benefits and adverse effects in treatment of several mental conditions. Contradictory reports can be found, as Bridge et al. (2007) found SSRIs to be significantly beneficial in reducing symptoms of MDD, Obsessive Compulsive Disorder (OCD) and non-OCD anxiety disorders. However Kirsch et al. (2002) describes fluoxetine, paroxetine and two other SSRIs not to be effective in patients with moderate or severe depression. Only the most severe cases showed significant results. However, the results in this might be attributed to a decrease in placebo effect, which is another interesting find to investigate further in the future. Meta analyses show controversial results as to whether the benefits outweigh the (harmful) side effects. The controversy mainly exists because of high risk of bias in studies caused by incomplete data, selective outcome, industry sponsoring and insufficient blinding. (Jakobsen et al., 2017)

Tricyclic Antidepressants The operation of TCAs is similar to that of SSRIs, the reuptake of monoamines is inhibited by antagonist binding on monoamine transporters. Different is that TCAs work on both SERT and Norepinephrine Transporter (NET), thereby increasing serotonin and noradrenaline levels. Through a negative feedback mechanism via

α_2-autoreceptors, the increase in levels of noradrenaline causes a decrease in noradrenaline release. This leads to a weakening of neuron firing and metabolic activity. The antagonistic effect on postsynaptic receptors is greater than with SSRIs, causing more side effects. For this reason the prescription of TCAs has mostly been replaced by SSRIs. (Waller & Sampson, 2017) Still often prescribed is the TCA dothiepin (Kauffman, 2009).

Serotonin and Noradrenaline Reuptake Inhibitors Serotonin and Noradrenaline Reuptake Inhibitors (SNRI) also block SERT and NET and just as SSRIs they have a low affinity for postsynaptic receptors resulting in less side effects. (Waller & Sampson, 2017) Venlafaxine and Nefazodone are often prescribed SNRIs (Kauffman, 2009).

Norepinephrine Reuptake Inhibitors Norepinephrine Reuptake Inhibitors block the reuptake of noradrenaline through NET. The same negative feedback as described for TCAs occurs, resulting in desensitization of the noradrenaline release mechanism. Because of elevated noradrenaline, serotonin is also elevated because noradrenaline stimulates somatodendritic α_1-adrenoreceptor. (Waller & Sampson, 2017)

3.1.2 Enzym inhibition by monoamine oxidase inhibitors

MAOIs work by inhibiting MAO, an enzyme that degrades monoamines in presynaptic nerve ends. Of MAO there are 2 types, A and B, of which MAO-A metabolizes serotonin, noradrenaline and dopamine. MAO-B metabolizes dopamine and tyramine. High tyramine intake in combination with MAOIs causes an increase in noradrenaline release, this in turn causes vasoconstriction, resulting in high blood pressure. The antidepressant Reversible Monoamine Oxidase Inhibitor is an MAOI specifically targeting MAO-A leaving MAO-B to remain to metabolize tyramine. (Waller & Sampson, 2017)

3.1.3 Ketamine

Ketamine hydrochloride functions as a N-methyl-D-aspartate receptor (NMDAR) antagonist, which is an ionotropic glutamate receptor. According to Berman et al. (2000) low-dose ketamine can serve as an antidepressant. The effects of ketamine are quick, they can be observed in hours after administration of the drug, and effective, a single dosage may last for a week. However, other NMDA receptor antagonists do not cause as strong of an antidepressant effect as ketamine does, which is cause to believe that the NMDAR inhibition is not the (only) cause of its antidepressant effect. Zanos et al. (2016) found that when ketamine is metabolized, this produces substances that through glutamatergic signaling and upregulation of AMPA receptors in the hippocampus have antidepressant actions. The ketamine metabolite pathway is efficient and produce little adverse effects (Zanos et al., 2016).

3.2 Alternative treatments

3.2.1 Sleep Deprivation

In depression sleep patterns exhibit differences from normal patterns. These changes entail prolonged latency, an alteration of sleep stages including abnormal waking periods, and patterns in REM sleep. An inverse relation has been determined between REM sleep latency or sleep efficiency and the severity of depression. (Borbely & Wirz-Justice, 1982) The hypothesis behind the alterations observed in sleep patterns in depression is a defect in circadian clock machinery. Total sleep deprivation of one whole night has been found to reduce depressive symptoms rapidly after treatment in 40-60% of all treatments, it is thought to provide a reset of the clock gene machinery. This effect however, will be reset by recovery sleep, resulting in depressive relapse in 50-80% of previously responding patients. (Bunney & Bunney, 2013)(Giedke & Schwärzler, 2002) It is important to take into account that sleep has an effect on many biological systems. A deprivation in sleep might cause a decrease in synaptic plasticity by suppressing neurogenesis and neuronal cell generation (Bunney & Bunney, 2013). Furthermore, it is important to note that chronic sleep deprivation can in some cases induce depression (Al-Abri et al., 2015). As stated before, a good diagnosis is essential to find the fitting treatment.

3.2.2 Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is a form of psychotherapy with the aim of improving mental health by altering behavior and emotional response. CBT has 3 main components: cognitive therapy, lifestyle modification and well-being therapy. The type of therapy is often done in combination with antidepressant medication and as a way of support after the ending of medication, the latter proves to be more effective than clinical management after discontinuation of drug therapy. (Fava et al., 1998)

3.2.3 Electroconvulsive Therapy

In Electroconvulsive Therapy (ECT) electricity is applied to the scalp to induce seizure-like activity. As a result, cortical GABA concentrations are increased, serotonergic function is improved and the HPA-axis is affected. Functional brain activity and neuronal structure have changed, synaptic plasticity has appeared to have improved. It has been reported that ECT is in many cases more effective than antidepressant medications, depending on the performance of the technique. Electrode location and dosage of electricity are crucial. Despite its effectiveness, the use of ECT is often postponed after alternative options have been proven unsuccessful. Reason for this is relatively more severe side effects. The most common unwanted effect is retrograde amnesia, extending to months or years before treatment. Other side effects are headache, muscle ache, nausea and fatigue. There haven't been any reports of anatomical damage due to ECT. (Lisanby, 2007)

3.3 Manic episode treatment

The alkaline metal lithium is a mood stabilizer to treat manic episodes in psychotic depression and bipolar disease. It can replace specific cations in certain cellular mechanisms, having blocking effects on transmitter and hormone release. Anticonvulsant drugs have a similar affinity for cation channels, but targeted to specific channels. Antipsychotic drugs also interfere with cation channels, making them have receptor-blocking qualities. Because of signal transduction blocking, lithium, anticonvulsants and anti-psychotics all have stabilizing properties. (Cookson, 2001)

4 Paradoxical effects of antidepressants

A debate has been going on about whether antidepressants, above all SSRIs, are mainly beneficial or harmful to patients with depression. It is difficult to separate the harmful effects of treatments from the destructive role of the disease itself since adverse effects from medication sometimes resemble disease symptoms. Through the use of placebo and real treatment, several studies have published proof of increase in suicide rates with . Juurlink et al. (2006) and Friedman & Leon (2007) state that an increase in risk of society is associated with SSRI during the first 4-6 weeks of treatment. An important sidenote, Bielefeldt (2016) found that antidepressants (SSRIs and SNRIs) can double the chance of a suicide in adult healthy volunteers. This portrays evidence of a good diagnosis. If a patient receives antidepressants and may improve after the first 4-6 week period, this cannot be confused with a patient who appears to not be depressed and will only decline after those first weeks.

4.1 Proposed mechanism

As mentioned, SSRIs work by increasing serotonin levels within minutes or hours after the medication is taken. Therefore it is puzzling that antidepressant effects may take weeks to commence. As many authors believe, there is a process going on that lets patients become activated before their mood improves, driving them to impulsive decisions one of which might be suicide (Friedman & Leon, 2007). Mann & Kapur (1991) already thought that multiple neurotransmitter systems might be involved in aggressive and suicidal behaviour. Their hypothesis involved a temporary decrease in presynaptic serotonin firing as a result of antidepressant administration. The hypothesis that a temporary decrease in neurotransmitter action is the cause of unexpected behaviour is further explained in 2015 by Fischer et al.

By selective blocking of glutamatergic pathways, Liu et al. (2014) discovered the role of glutamate in rewarding behaviour, learning and hedonic behaviour. When glutamate was absent, more anhedonic behaviour was observed. The impairment of the serotonergic component resulted in a decrease of motivational behaviour. According to Varga et al. (2009) serotonergic neurons in the raphe nuclei contain glutamate as well as serotonin. Thus, when a neuron is triggered, both serotonin and glutamate are released. The firing rate of a serotonergic neuron is controlled via 5-HT_{1A}-autoreceptor, a postsynaptic serotonin receptor. As described in section 3.1.1, the presynaptic membrane protein SERT transports serotonin from the synaptic cleft back into the neuron. This can be seen in figure 1. [1]

When an SSRI is administered and SERT is blocked, serotonin values in the synaptic cleft increase (figure 2A). Due to contstantly elevated levels of serotonin, 5-HT_{1A}-autoreceptors become desensitized, resulting in a decrease in neuronal firing, a reduce in release of serotonin and glutamate (figure 2B) . Because of SSRI effective inhibition of serotonin reuptake, serotonin levels will stay high. However, if glutamate levels fall, it takes a few weeks to restore this decline. As shown in figure 3, after a few weeks, sensitivity of 5-HT_{1A}-autoreceptors return to pre-treatment values. Normal firing returns, so glutamate will be released. Glutamate receptors GluR6 and AMPA3 might even be upregulated due to decreased levels of glutamate of the preceding period. This may result in a sensitization for glutamate and an increase in effectiveness of the medication. (Fischer et al., 2015)

[1] Images created with biorender.com

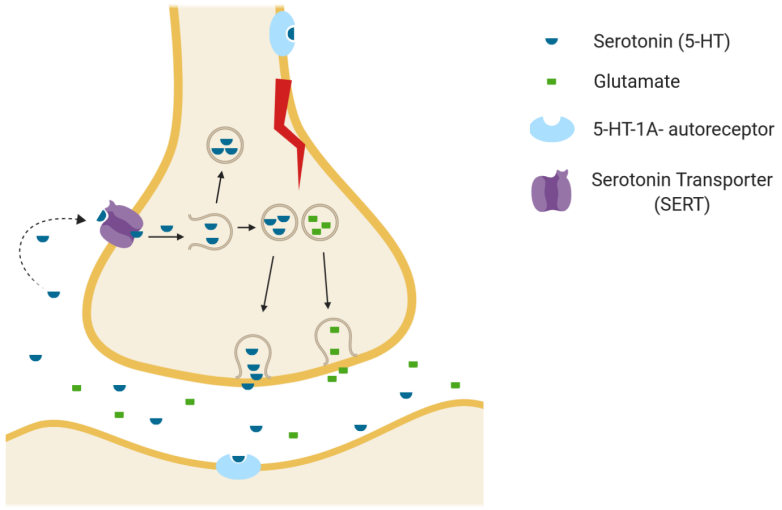

Figure 1: Before administration of SSRI.

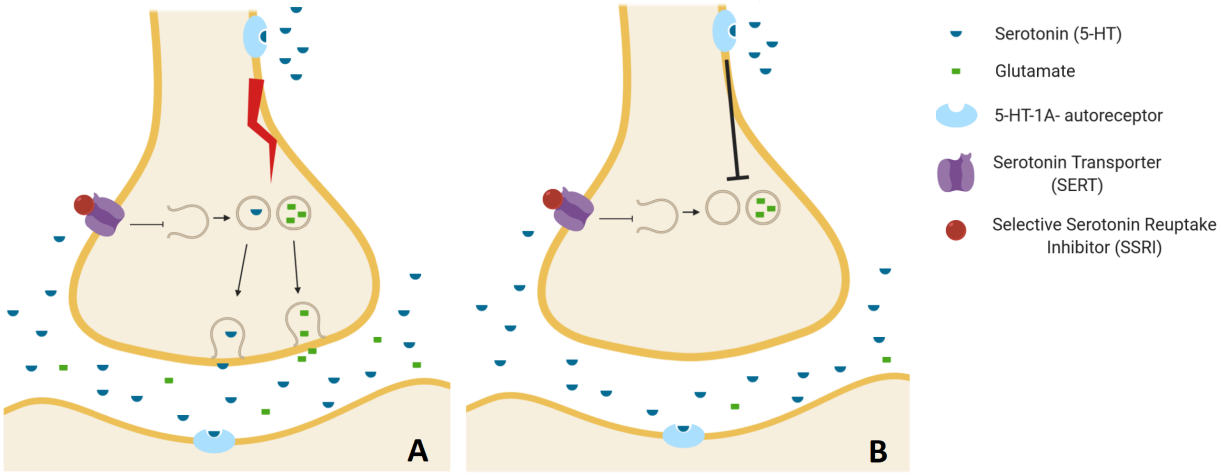

Figure 2: A few minutes/hours after administration of SSRI.

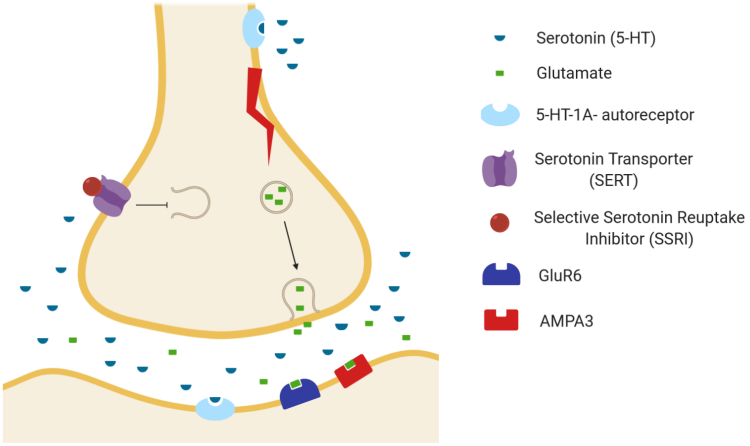

Figure 3: A few weeks after administration of SSRI.

The restoration of glutamate and its role in positive emotions suggests that the above described mechanism may play a role in the deterioration of depression during the first weeks of treatment. Other indicators are genes encoding for glutamate receptors that have associations with suicidal thoughts in patients treated with SSRIs. The genes GRIA3 and GRIK2 encoding for GluR6 and AMPA3 respectively, are upregulated during the first weeks of treatment with SSRIs. (Laje et al., 2007) Treatment with ketamine that goes via an increase in AMPA receptors, shows immediate positive effects (Berman et al., 2000). Taken all together, glutamate and its receptors show to play an important role in the immediate beneficial effects for treatment of depression.

Genetic basis behind suicidality ideation has been found to play a role in neurotransmitter pathways, synaptic plasticity, neuroendocrine substances or neuroinflammation. For these processes Nader Perroud (2011) summarizes the involved genes. ADRA2A is an adrenergic receptor gene. ADRA2A may not only predict suicidal behaviour in non-treatment situations, but also plays a role in treatment-resistance and even increase suicidal ideation, mostly in male patients (Perroud et al., 2009). Other predictor genes found by Perroud (2011) are GDA (encodes for glutamatergic pathways, as well as GRIA3 and GRIK2), CREB1, BDNF and NTRK2 (encode for neurotropic and synaptic plasticity), IL28RA and FKBP5 (encode for inflammatory mechanisms and HPA-axis systems).

5 Discussion and implications

Major Depressive Disorder is a complex disease with many uncertainties. Although there are some hypotheses on mechanisms behind the dysfunctionalities in the brain, such as the monoamine hypothesis and synaptic plasticity and brain structure aberrations, these are not conclusive. This makes proper diagnosis hard and therefore it is difficult to develop suitable medication or alternative treatments. There are many treatments already available and although there are difficulties in effectiveness and efficiency, they provide a beneficial solution for a majority of the patients (Gibbons et al., 2006). However, since there is room to improve and it remains important to continue research on MDD and its underlying mechanisms and effective treatments.

This continuation of research might also shed more light on the mysterious paradoxical effects of some antidepressant medications. So far, SSRIs have mostly shown to cause an increase in depressive symptoms and suicidal ideation. The mechanism as described by Fischer et al. (2015) where immediate glutamate depletion due to SSRI administration causes patients to worsen, is likely to play an important role. However, there may be many unseen contributors. Vulnerability to depression in general but reaction to antidepressants in particular may not be overlooked. Genetic predictors could help in determination of the risk for depression and response to treatment in an individual.Furthermore, neuroendocrine, immunological and external factors could influence the monoamine pathways and genetic activation or inhibition in ways that are unseen so far.

A few questions raise from Fischer et al. (2015) on the difference between serotonin and glutamate. Glutamate levels drop due to the decline in 5-HT_{1A}-autoreceptor sensitivity. Glutamate is restored after several weeks, because of a negative feedback mechanism. Serotonin levels initially do not drop because of a blockage of SERT. Is there no feedback mechanism for serotonin levels, causing them to eventually also drop? Will serotonin be metabolized? Or else, what are the long-term effects of these high levels of serotonin? Another question is how desensitization of 5-HT_{1A}-autoreceptors due to high serotonin takes place. Possibilities might lie in counteracting the desensitization in order to restore serotonergic neuronal firing rates much quicker. And for glutamate the question might be asked if there exist a transporter protein that may transport glutamate from the synaptic cleft back into the cell, like SERT does for serotonin. Fischer mentions VGLUT3 and VMAT2 as transporter proteins for transport of vesicles containing glutamate and serotonin respectively. This transport takes place from the neuronal cytosol to the membrane. Discovery of an extracellular to intracellular glutamate transporter might provide insight in the system. Blockage of a glutamate transporter might result in an improvement of symptoms for depressive patients.

There is an important note in studies that show an association between antidepressant medication and suicides. Patients with more severe depression were more likely to receive medication instead of a placebo due to ethical reasons. Also, the more severely depressed people received higher dosages. These patients were already at a higher risk of suicide at the start of the trial. This might result in showing a strong link between antidepressants and suicide, when not properly corrected for. (Olfson et al., 2006)

As a result of the concern about the paradoxical effect of antidepressant use, Stone et al. (2009) conducted a meta-analysis of age in relation to suicide risk after antidepressant administration. In children and adolescents (ages under 25) a significant association between antidepressant medication treatment and suicide attempts or completed suicide was found, which was a similar result from other studies (Olfson et al., 2006). No difference between SSRI and TCA was found in this regard (Martinez et al., 2005). However, as Gibbons et al. (2006) note, an important factor in depression and usage of antidepressants in children and adolescents is the influence of the parents, genetically and

through behaviour. This may again result in an unfair representation in the chance of suicide related to the use of antidepressant medications.

Some important notes need to be made about the conducted research that is used in this report. There have been many discrepancies in the methods for different studies. A different dataset was used between the Olfson and Gibbons studies, using a group of different ages, a different time frame, Gibbons analysed only SSRI usage while Olfson looked at all antidepressants (Olfson et al., 2006) (Gibbons et al., 2006). It is hard to dispute antidepressant prescription from actual use. A definition of depression and suicide have to be well-established. The fact that generally only a small number of completed suicides is observed and it is hard to define suicide related thoughts, makes statistical analysis difficult. (Quitkin & Klein, 2000)

To determine the safety of antidepressant medication it is important to not only take into account the risk of an increase in suicidal thoughts, but also side effects, both short- and long-term and risk of overdose. The beneficial and harmful effects need to be weighed out for each available treatment. This balance can be used by clinicians to provide aid in deciding how to treat a patient. The patient needs to receive a personalized advice, preferably including a genetic risk analysis on response to the medication. In any case, close monitoring of well-being of MDD patients is important. When an antidepressant with increased risk of suicidal ideation in prescribed to a patient, the use of tranquilizers might help (Fischer et al., 2015).

In conclusion, more research is needed in different areas regarding MDD. The mechanisms that underlie or aggravate the depression as well as effectiveness and efficiency of medications and alternative treatments, specifically side effects of medications and how to prevent or relieve them. Glutamatergic pathways and genetic background for the mechanisms in which glutamate is involved, show promising prospects to play an important role in medications in the future.

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