Side effects of antidepressants

Elia, Harel

University of Zagreb
School of medicine

Harel Elia

Side effects of antidepressants

Graduate thesis

Zagreb, 2022

This graduate thesis was made at the Department of Psychiatry at the University hospital center ”Sestre milosrdnice” Zagreb, under the guidance of Branka Aukst Margetić, Assist. Prof. MD, PhD and was submitted for evaluation in the academic year 2021/2022.

Mentor: Branka Aukst Margetić, Assist. Prof. MD, PhD

Abbreviations:

WHO - World Health Organization

OCD- obsessive-compulsive disorder

CBT - cognitive behavioral therapy

5-HIAA - 5-hydroxyindoleacetic acid

5-HT - 5-hydroxytryptamine.

MDD - major depressive disorder

NE - noradrenalin

TCA - tricyclic antidepressant

MAOI - monoamine oxidase inhibitor

SSRI - selective serotonin reuptake inhibitors

NDRI - Noradrenalin and dopamine reuptake inhibitors

SNRI - Serotonin and noradrenalin reuptake inhibitors

NRI - Noradrenalin reuptake inhibitors

MOR - μ-type opioid receptor

FDA - Food and Drugs Administration

SARI - serotonin receptor antagonists and reuptake inhibitors

SERT - serotonin transporter

NDSAID - non steroidal anti-inflammatory drug

Table of contents:

1. Summary **5**
2. Introduction **6**
3. Indications for the usage of antidepressants **7**
3.1. Depression: **7**
3.2. Anxiety disorders: **9**
4. Antidepressants **10**
4.1 Tricyclic antidepressants **11**
4.2. Monoamine oxidase inhibitors **12**
4.3. Selective serotonin reuptake inhibitors **14**
4.4 Noradrenaline and dopamine reuptake inhibitors **17**
4.5 Serotonin noradrenalin reuptake inhibitors (SNRI) **18**
4.6. Noradrenaline reuptake inhibitors (NRI) **19**
4.7.1 **Atypical antidepressants** 20
4.8. Serotonergic syndrome **25**
5. Conclusion: **26**
6.Acknowledgments: **27**
7.References **28**
8. Biography: **34**

1.Summary

Title: Side-effects of Antidepressants

Author: Harel Elia

Depression and anxiety are the most common mental health illnesses worldwide. According to large population-based surveys, up to 33.7% of the population are affected by an anxiety disorder during their lifetime (1) and, according to the WHO about 6% of the population is affected by depression worldwide.

Medications have a key role in controlling and reducing the symptoms of these mental conditions together with psychotherapy technique.

Unfortunately, the side effects of such medication tend to appear before the desirable outcome of their usage start to effect the patients. This phenomena cause non-compliance in the patients' population.

Since many of these patients have comorbidities and therefore are more likely to be treated with more than one medication, it is more likely for them to experience those undesirable side effects.

It is of crucial importance that healthcare providers will be aware of the side effects profile of these medication in order to change the prescription to a lower dose or an alternative medication.

The benefits of a well-treated patient are not only to the individual but to the family, community and the economy as the outpatient setting are allowing the patient to maintain normal lifestyle and the therapy is many folds cheaper than hospitalization due to these conditions or their complications.

Key words: antidepressants, depression, anxiety.

2. Introduction

The beginning of psychiatry as a medical specialty is dated to the middle of the nineteenth century. Its development was slower than that of the rest of medical specialities due to multiple reasons: view that psychical illnesses have supernatural causes, complexity of the brain, inability to make research due to ethical reasons. In 1950s we have the development of first psychopharmacological treatments. The first antipsychotic chlorpromazine and after that first antidepressants imipramine and iproniazide were discovered. However, research and experiments in psychiatry are highly restricted due to ethical and legal reasons and the progress today is associated with the development of neuroscientific research.(1)

Depression, together with anxiety, is one of the most common mental disorders in the world. The awareness to this pathology has increased significantly in the last few decades, but the treatment has not change much. Psychotherapy and antidepressants are the main strategies in the treatment of depression. The side effects of antidepressants are one of the major obstacles in the treatment of depression. Although the safety and tolerability of antidepressants have improved considerably over the past two decades, up to 70% of patients taking antidepressants are non-compliant, as a result of either missed doses or premature discontinuation. (2,3)

Despite the development of new antidepressant classes that mitigate some of the side effects of first antidepressants, their side effects are still common and problematic. The majority of patients treated with antidepressants experience at least one or even several side effects. These side effects often create barriers to achieving depressive remission, as well as to preventing relapse and recurrence and are compromising the overall effectiveness of the treatment. About one quarter of patients discontinue their antidepressants because of side effects. Even if patients continue on antidepressant therapy, due to them, they may experience diminished quality of life.

In the following review I describe the antidepressants' most common side effects by their class and mechanism as well as their management.

Firstly, I shortly review main indication areas for the prescription of antidepressants. Then, I review antidepressants by class and mechanism of action, mention the main side effects, their prevalence and significance for the quality of life. I also describe management of particular side effects.

3. Indications for the usage of antidepressants

Despite the name "antidepressant" the use of these drugs is not only to treat the various types of depression, but also, they are used for the treatment of different types of anxiety disorders. They are also used for treatment of anxiety and depressive symptoms when they appear in some other disorders like schizophrenia. In addition, antidepressants can be used to treat somatic pain symptoms. (4)

3.1. Depression:

Depression is a common mental disorder that is being diagnosed more often than ever before.

Depression is a mood disorder that manifest as persistent feeling of sadness and loss of interest in previous enjoyable life activities. The American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies the depressive disorders into: Major depressive disorder and includes new categories as Persistent depressive disorder (dysthymia), Disruptive mood dysregulation disorder, Premenstrual dysphoric disorder and Depressive disorder due to another medical condition. (5)

3.1.1. Diagnosis of depression:

The common features of all depressive disorders are sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function.

The WHO defines depression as persistent sadness and a lack of interest or pleasure in previously rewarding or enjoyable activities. Other common manifestations are sleep

disturbances changes in appetite (anorexia, hyperorexia) tiredness and poor concentration. The criteria according to ICD-10 are presented in table 1.

	Symptoms of major depressive episode ICD-10
typical	Depressive mood
	Loss of interest and pleasure
	Decrease in energy or proneness to fatigue
additional	Loss of self-confidence or self-respect
	Self-reapproaching or quilt feeling
	Recurrent thoughts of death or suicide
	Problems in thinking and concentration, indecision
	Agitation or retardation
	Sleep disturbance
	Disturbance of appetite and change of body weight

Table 1. ICD-10 criteria for Major depressive episode

3.1.2. Etiology:

The leading hypothesis about the cause of depression is associated with changes in the serotonergic neural function in the central nervous system. These findings include the following: (a) reduced cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin (5-HT) in drug-free depressed patients; (b) reduced concentrations of 5-HT and 5-HIAA in postmortem brain tissue of depressed and (or) suicidal patients; (c) decreased plasma tryptophan concentrations in depressed patients and a profound relapse in remitted depressed patients who have responded to a serotonergic antidepressant when brain tryptophan availability is reduced. (6) Similarly, norepinephrine (NE) dysregulation have been identified in patient with MDD.

Postmortem studies have shown a selective increase in the high-affinity conformation of the brain α2A adrenoceptors as well as decreased binding to NE transporters in the locus coeruleus of depressed patients. The latter finding suggests a compensatory down regulation of this transporter protein in response to an insufficient availability of the NE at the synaptic level. Recent studies also show dysregulation of dopamine in depression (7)

3.1.3. Epidemiology:

Depression affects more than 264 million people worldwide. According to the global health data exchange it is estimated that 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years. At its worst, depression can lead to suicide. Over 700,000 people die due to suicide every year. Suicide is the fourth leading cause of death in 15-29-year-olds. (8,9)

3.2. Anxiety disorders:

Anxiety disorders represent one of the major groups of disorders seen in psychiatry, and in the rest of medicine as well. Over several decades, the classification of these disorders had not changed dramatically, although advances in neuroscience and therapeutics have focused attention on how the anxiety disorders are grouped. (10,11) Most categories of anxiety disorders are treated with antidepressants, but the dosage can differ from dosage in depression.

The categories of anxiety disorders where antidepressants are used are the following:

Generalized anxiety disorder: It is characterized by chronic anxiety, exaggerated worry and tension with little to no provocation.

Panic disorder: It is characterized by unexpected episodes of intense fear accompanied by somatic symptoms (chest pain, palpitations, shortness of breath etc.). We distinguish panic disorder with agoraphobia and without agoraphobia.

Agoraphobia - is state characterized by fear or anxiety about multiple situations in which escape might be difficult or that panic-like symptoms might develop. (11)

Social anxiety disorder. Characterized by anxiety and excessive self-consciousness in everyday social situations.

Specific phobia: It is characterized by overwhelming anxiety and fear from different situation. Common phobias are aerophobia (fear of flights) arachnophobia (fear of spiders) claustrophobia (fear of confined or crowded places) etc. The treatment is based on psychotherapy and antidepressants are used mostly with comorbidity.

Obsesive –compulsive disorder (OCD) is a common, chronic, and long-lasting disorder in which a person has uncontrollable, reoccurring thoughts (obsessions) and/or behaviors (compulsions) that he or she feels the urge to repeat (12). To be diagnosed as disorder the symptoms have to take up at least an hour a day, the patient is not able to stop them and interfere with work, social life, or another part of life. The dosage of antidepressant is much higher in (OCD) than in treatment of depression.

Posttraumatic stress disorder- is also categorized under stress disorder in ICD-10 classification. This is the only disorder in psychiatric classification whose etiology is based on a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, or rape or person have been threatened with death, sexual violence or serious injury. The dosage of antidepressants is also higher that in treatment of depression (13)

Eating disorders- bulimia nervosa and anorexia nervosa can also be treated with antidepressants, mostly of selective serotonin reuptake inhibitors. The dosage of those drugs is higher than in depression and anxiety. (14)

Treatment of pain- Pain is also indication for the usage of some categories of antidepressants e.g. serotonergic and noradrenaline reuptake inhibitors and tricyclic antidepressants. (15)

4. Antidepressants

Antidepressants are the most effective pharmacological intervention that modern medicine has to offer to patients that are suffering from depression and anxiety. There are several classes of antidepressants and they can be divided to monoamine uptake inhibitor (tricyclic antidepressants (TCA), monoamine oxidase inhibitors (monoamine oxidase inhibitors

(MAOI), selective serotonin re-uptake inhibitors (SSRI). Norepinephrine and dopamine re-uptake inhibitors (NDRI)) serotonin and noradrenalin reuptake inhibitors (SNRI) and atypical antidepressants. (3)

4.1 Tricyclic antidepressants

Trycyclic antidepressants were approved for clinical usage in 1957. and imipramine was the first drug discovered. (16) After the introduction of imipramine the physiopathological role of biogenic amines in depression was demonstrated and monoamine hypothesis developed.

This group contains the medications- amitriptyline, clomipramine, desipramine, dosulepine, doxepine,imipramine, lofepramine, nortryptyline, protriptyline, trimipramine maportiline and mianserin. (3) This class of drugs changed treatment of depression completely and lead to development of the hypotheses that explained the etiology of depression.

4.1.1. Mechanism of action:

TCA inhibit the neuronal re-uptake of noradrenaline and serotonin, thereby increasing their concentration within the synapses and enhancing neurotransmission. Their efficacy for the reuptake of the two types of neurotransmitters (serotonin and noradrenalin) varies and this results in different frequencies and intensities of side effects. They are also competitive antagonists at the muscarinic, histaminergic, and alpha 1 and 2 adrenergic receptors, which results in their characteristic side-effect profile. Amitriptyline, imipramine, and doxepin have the most anticholinergic activity, whereas nortriptyline and desipramine are less anticholinergic activity. (3)

4.1.2. Side-effects:

Anticholinergic side effects include dry mouth, constipation, urinary retention, blurred vision, confusion, and delirium. Narrow-angle glaucoma can be worsened.

Cardiac effects: TCA may slow cardiac conduction, causing intraventricular conduction delay, atrioventricular block, flattened T waves, depressed ST segments, and prolonged QT intervals. All tricyclic antidepressants can cause tachycardia, which is one of the most common reasons for stopping them. Nortriptyline is the least likely to cause orthostatic hypotension. Because of cardiotoxicity, an overdose of as little as 1 week's dosage of medication can be fatal. (17)

Sedation is the most common side-effect of tricyclic antidepressants and is a result of anticholinergic and antihistaminergic effects. Doxepin has the highest antihistaminergic activity among tricyclic antidepressants.

Weight gain and sexual side effects are also common. (17)

A discontinuation syndrome is mostly related to cholinergic and serotonergic rebound. It is characteristic of these symptoms that they appear 1-4 days after reduction of the dose or the last administration of the drug. The syndrome may include: influenza-like symptoms, psychic symptoms, gastrointestinal symptoms, sleep disorders, equilibrium disorders, sensory disturbances, extrapyramidal symptoms and other symptoms. After prolonged treatment, tricyclic antidepressants should be tapered gradually over several weeks. Discontinuation syndrome appears practically with all antidepressant drags but is more pronounced in tricyclics and MAO inhibitors.

4.2. Monoamine oxidase inhibitors

MAO inhibitors as a class were introduced when iproniazid was clinically approved in 1957. MAOIs, although effective, generally have been replaced by newer antidepressants that are safer and cause fewer side effects. Still, an MAOI is a good option for some people. In certain cases, an MAOI relieves depression when other treatments have failed. Monoamine oxidase is enzyme that catalyze oxidative deamination of neurotransmitters such as serotonin, dopamine, norepinephrine, and epinephrine. Two isoforms of MAO have been identified: MAO A that has high affinity for serotonin and to a lesser degree norepinephrine and MAO-B that more effectively metabolizes phenylethylamine and

benzylamine. Epinephrine, dopamine, tryptamine, and tyramine are metabolized to varying degrees by both MAO-A and MAO-B. Drugs that inhibit this enzyme called monoaminoxidase inhibitors (MAOI) are divided to three groups, based on their selectivity for MAO A or MAOB. (18)

Non-selective MOAI – phenelezine, tranylcyptomine and isocarboxazide.

Selective MAOI type A - moclobemide.

Selective MAOI type B - rasagaline and selegiline. The former are used in the treatment of Parkinson disease, but selegilin in higher dosages and transdermal formulation shownunsecetivitu for MAO A and B and can be used as antidepressant. (18)

4.2.1. Mechanism of action:

Inhibition of the enzyme monoamine oxidase from removing the neurotransmitters norepinephrine, serotonin and dopamine from the synaptic cleft, results in their accumulation.

Monoamine oxidase inhibitors are very effective antidepressants, but dietary restrictions and the risk of hypertensive crises limit their use. Besides neurotransmitters norepinephrine, serotonin and dopamine from the synapse it also metabolises tyramne, a derivate of amino acid tyrosine.

The consumption of tyramine-containing foods like yeast, red wine and aged cheese thereby results in its accumulation and a possible dangerous rise in blood pressure. This effect is known as “tyramine effect” or “cheese effect”. Monoamine oxidase takes several weeks to be replaced thereby the danger of such an interaction persists for up to two weeks following discontinuation of the MAOI. (3)

The selective reversible inhibitors of MAO-A (RIMAs) moclobemide reversibly inhibits MAO and through dissociation of the inhibitor from its combining site, is safe in in the case of tyramine ingestion (18).

4.2.2. Side effects:

Orthostatic hypotension, the most frequent side effect, is secondary to alpha-1 adrenergic blockade. The exact mechanism is not known but likely involves elevated norepinephrine at presynaptic alpha-2 receptors.

Dizziness and reflex tachycardia may also occur.

Antihistaminergic activity might lead to weight gain and sedation.

Hypertensive crises are usually induced by consuming food rich in tyramine or by medications with sympathomimetic activity. Headache, stiff neck, sweating, nausea, and vomiting characterize the prodromal phase. This could be followed by autonomic instability, elevated blood pressure, cardiac arrhythmia, coma, and death.

Sexual dysfunction, hepatotoxicity, and pyridoxine deficiency have also been reported. (17)

4.3. Selective serotonin reuptake inhibitors

SSRIs were first introduced in clinical practice about 30 years ago, and there is an immense continual increase in their use. In comparisons to TCI and MAOI they were much better tolerated and safer with similar efficacy in treatment of mild and moderate depression (19). Unlike TCAs, SSRIs do not cause cardiac conduction abnormalities in overdose and have low propensity to cause seizures (20) Thus, development of the SSRIs was an important milestone in the treatment of depression. Treatment is now highly common within the general population, with estimates that up to 13% of the US population use it. (21)

They are used for the treatment of depression but as well for treatment of anxiety disorders like: generalized anxiety disorder, obsessive compulsive disorder, panic disorder, posttraumatic stress disorder. This group contains the medications: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

4.3.1 Mechanism of action:

“Inhibit the neuronal reuptake of serotonin by specifically binding to 5-HT transporter proteins on the synaptic membrane. Their effects on noradrenaline or dopamine reuptake are minimal”. (3) Affinity of SSRIs to bind to various neuroreceptors is very low. That explains their more favorable side-effects profile with comparable efficacy in outpatients with mild and moderate depression (7). Mechanism of how the SSRI works is shown on Figure1.

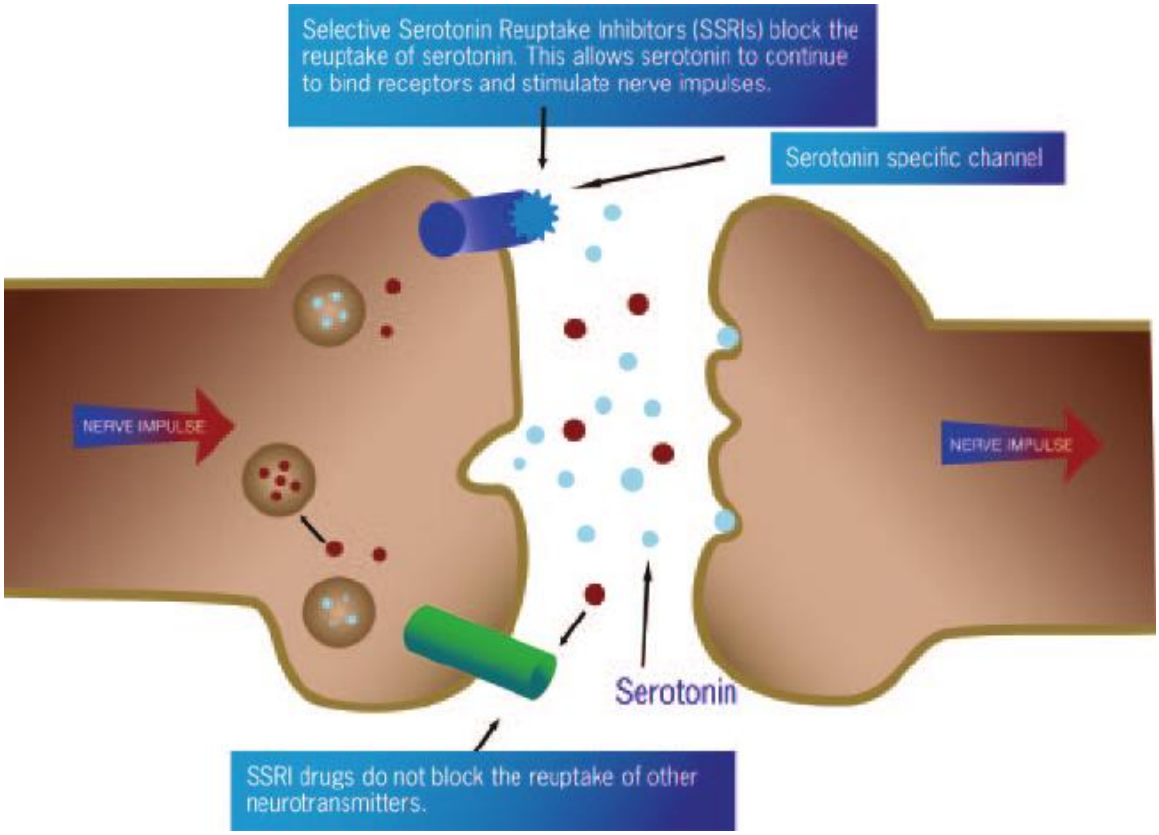

Figure1. Science, serotonin, and sadness: The biology of antidepressants - A series for the public - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Unlike-previous-anti-depressant-treatments-selective-serotonin-reuptake-inhibitors_fig4_5878197 [accessed 14 Feb, 2022]

4.3.2 Side-effects:

Serotonin reuptake inhibitors are generally well tolerated. However, approximately 15% of patients cannot tolerate certain side effects and therefore may stop taking the drug.

Sexual dysfunction is the most common side effect of all serotonin reuptake inhibitors. Although psychiatric illnesses in themselves can affect sexual desire and performance, so can the drugs used to treat the illness. Delayed ejaculation, anorgasmia, and decreased

libido can occur in up to 60% of patients, and the effects continue as long as the drug is taken. (17) Within the class of SSRIs, erectile dysfunction, vaginal lubrication difficulties, and decreased libido in both sexes are most common with paroxetine, particularly in the first month of therapy (22).

Sertraline and fluvoxamine may cause more gastrointestinal side effects more than other serotonin reuptake inhibitors. Within the first 2 weeks of treatment patients may experience nausea and diarrhea that are dose-related and usually resolve. Starting the medication at a low dose, giving it in divided dosing and with food usually alleviates nausea.

Constipation and dry mouth tend to be more common with paroxetine because of its anticholinergic activity.

Anorexia is most common with fluoxetine and occurs early in the treatment. It is probably related to activation of 5-HT2C receptors. However, with time this suppressant effect on appetite is lost.

Indeed, serotonin reuptake inhibitors have the potential to cause weight gain, possibly due to desensitization and down-regulation of the serotonin receptors associated with appetite control. Antidepressants among this class differ based on potential to cause weight gain, Paroxetine has shown to cause most significant weight gain.

Central nervous system side effects Of SSRIs include anxiety, insomnia, sedation, nightmares, and extrapyramidal symptoms.

Patients may experience increased anxiety, most commonly early in treatment. Slow dosing is strategy to avoid it. Sleep disturbances, either insomnia or somnolence, have been reported in about 25% of patients taking serotonin reuptake inhibitors. Fluoxetine is more likely to cause insomnia than is paroxetine, which is more likely to cause sedation. Others tend to lead equally to somnolence or insomnia.

Headache, nightmares, and vivid dreams have been reported in a minority of patients. These side effects often resolve within a few weeks and rarely lead to a change in medication.

In rare cases, serotonin reuptake inhibitors can cause extrapyramidal side effects, including akathisia. Such adverse effects are not due to dopamine receptor blockade, but rather to increased serotonin at the synaptic levels, mediating inhibition of the release of dopamine through one of the presynaptic serotonin receptor subtypes.

Serotonin reuptake inhibitors inhibit platelet function and may prolong bleeding. Several reports have indicated an association between the use of these drugs and bleeding disorders ranging from bruising and epistaxis to more serious conditions such as gastrointestinal bleeding. (23)

Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH) hyponatremia manifesting as confusion, drowsiness, dizziness and seizures was also described with this class of antidepressants.

Discontinuation syndrome can occur if a serotonin reuptake inhibitor with a short half-life such as paroxetine or fluvoxamine is abruptly stopped. Patients may experience dizziness, nausea, weakness, insomnia, anxiety, irritability, and headache. These symptoms tend to be transient and resolve spontaneously within a week. Slowly tapering serotonin reuptake inhibitors over a couple of weeks can help prevent this syndrome. Fluoxetine is less likely to cause this syndrome because of its long half-life. Indeed, fluoxetine has been used to treat the discontinuation syndrome caused by other serotonin reuptake inhibitors. (17)

4.4 Noradrenaline and dopamine reuptake inhibitors

NRDI are less likely to cause the common side- effects of weight gain and decreased libido that are associated with SSRIs.

Bupropion is the only medication on this group.

4.4.1. Bupropion:

Bupropion is also considered as an atypical antidepressant.

3.4.1.1 Mechanism of action:

Bupropion is thought to work by inhibiting norepinephrine reuptake and dopamine neurotransmission. It also has an active metabolite that mediates antidepressant efficacy by blocking reuptake of norepinephrine and dopamine. (3)

4.4.1.2 Side-effects:

The main side-effects of bupropion are insomnia, headache, tremors, and nausea.

Increased irritability and agitation may also occur.

Seizures. The extended-release formulation carries a seizure risk of about 0.4% at a dose of 400 mg per day. Physicians should avoid prescribing this medication to patients who are prone to having epileptic seizures such as heavy alcohol use, or eating disorders; or with benzodiazepine withdrawal, head trauma, or organic brain syndrome. (17,24)

4.5 Serotonin noradrenalin reuptake inhibitors (SNRI)

This group contains the medications duloxetine and venlafaxine.

4.5.1. Mechanism of action

Drugs from this group inhibit the neuronal re-uptake of serotonin and noradrenaline at neuronal ends, thereby increasing both levels within the synapse. (3)

4.5.2 Side-effects

The most common side-effects reported in placebo-controlled clinical trials were nausea, dry mouth, constipation, fatigue, decreased appetite, and sweating. nausea is most common adverse event. Sexual dysfunction was more common with SNRIs than with placebo. However, the rate appears to be less than with serotonin reuptake inhibitors. Initial insomnia, irritability, anxiety, nervousness, and restlessness were also reported. Duloxetine was associated with an increased risk of mydriasis and should be used with caution in controlled narrow-angle glaucoma. Treatment with SNRIs was associated with increased blood pressure. Therefore, one should measure blood pressure before starting SNRIs and periodically monitor it throughout treatment especially when using venlafaxine extended release at doses of 225 mg or more er day. SNRIs should not be used in combination with

monoamine oxidase inhibitors and can be used only at least 14 days after stopping one of these drugs. If duloxetine is stopped, it should be tapered gradually to avoid discontinuation side effects. (17)

4.6. Noradrenaline reuptake inhibitors (NRI)

This group contains the medications reboxetine. Maprotiline and atomoxetine are often categorized with tricyclic antidepressants but have predominantly noradrenaline reuptake inhibition.

Reboxetine is a drug used for the acute treatment of major depression and for maintenance therapy of depression.

Maprotiline is a tetracyclic antidepressant used to treat depressive illness, major depressive disorder, bipolar disorder, and anxiety associated with depression.

4.6.1 Mechanism of action:

Medications from this group inhibit the re-uptake of the neurotransmitters norepinephrine (noradrenaline) by blocking the action of the norepinephrine transporter, which leads to increased extracellular concentrations of the two neurotransmitters. (3)

4.6.2 Side-effects:

Noradrenergic antidepressants typically cause minor changes in blood and heart rate, sweating and insomnia. Drugs from this class are less likely than selective serotonin reuptake inhibitors (SSRIs) to cause sexual dysfunction, but more likely to cause urinary hesitancy. (22)

The adverse effect profile of maprotiline is similar to that of the tricyclic antidepressants, except that rashes are about twice as frequent with maprotiline as with amitriptyline or imipramine. The most frequent adverse reactions are anticholinergic effects and sedation. Data suggest less frequent and severe anticholinergic side effects with maprotiline than with amitriptyline. Maprotiline may be less likely to induce orthostatic hypotension and tachycardia than standard tricyclic antidepressants, but clinically important differences in cardiovascular effects remain to be conclusively demonstrated (25)

1.7. Atypical antidepressants

An atypical antidepressant is any antidepressant medication that acts in a manner that is different from that of most other antidepressants. Recent research has shown that the monoamine theory of depression, changes in the serotonergic and noradrenergic neural function in the central nervous system, may not be the only cause of depression but other etiologies may be the reason for depression.

Atypical antidepressants include mirtazapine, agomelatine, mianserin, nefazodone, opipramol, tianeptine, trazodone and vortioxetine

4.7.1. Mirtazapine:

4.7.1.1. Mechanism of action:

Mirtazapine is a presynaptic alpha 2 adrenergic receptor antagonist and a potent antagonist of serotonin 5-HT2 and 5-HT3 Receptors. It has very little effect on 5-HT1 receptors. Therefore, mirtazapine directly increases norepinephrine release and, indirectly, serotonin release. It also blocks histamine receptors and has minimal affinity for muscarinic and alpha-1 adrenergic receptors. (3)

4.7.1.2 Side-effects:

Weight gain in one of the main side-effects. Mirtazapine can increase appetite and carbohydrate craving. This may lead to significant weight gain if not monitored closely. It may also increase cholesterol and triglyceride levels. (26)

Liver function tests, especially alanine aminotransferase, can be mildly elevated.

Neutropenia has developed in rare cases. This hematologic condition is more likely to occur in patients with other risk factors for neutropenia. (27)

Dizziness, dry mouth, constipation, increased appetite, and disturbing dreams have also been reported. Mirtazapine does not tend to cause sexual dysfunction. (17)

4.7.2 Tianeptine:

Structurally, tianeptine is classified as a tricyclic antidepressant (TCA), however, it possesses different pharmacological properties than typical tricyclic antidepressants. (28)

4.7.2.1 Mechanism of action:

Tianeptine acts as a full agonist at the μ-type opioid receptor (MOR) (29,30). In addition to its actions on the opioid receptor, previous studies have showed its action to its effect on the serotonin receptors, dopamine (D2/3) receptors and glutamate receptors. (31,32)

For who Patients cannot tolerate SSRI or TCA tianeptine is a well-tolerated and effective antidepressant. It could serve as a useful alternative, and improve the low compliance with treatment in patients with major depression and anxiety. (33)

4.7.2.2 Side-effects:

The most common adverse effects are rare and include nausea, constipation, abdominal pain, headache, dizziness and changes in dreaming. Anticholinergic effects occur less often with tianeptine than with tricyclic agents. Hepatoxicity is rare as it is excreted through kidneys. (34)

4.7.3 Agomelatine:

Sleep disturbances are often associated with depression and mood disorders, and certain manipulations of the sleep-wake cycle are effective as therapeutic interventions in the treatment of depression. (35)

Agomelatine is closely related, structurally, to melatonin, which regulates the sleep-wake cycle. It is generally considered safe, one that could be recommended to patient with narrow angle glaucoma.

4.7.3.1 Mechanism of action:

Agomelatine is a potent agonist at melatonin receptors and an antagonist at serotonin-2C (5-HT2C) receptors (36).

4.7.3.2 Side-effects:

Dizziness, gastrointestinal and cutaneous disorders have been observed, but are milder in comparisons to SSRI. Agomelatine is probably hepatotoxic. (37)

4.7.4 Vortioxetine:

Vortioxetine is an atypical antipsychotic and antidepressant indicated for the treatment of major depressive disorder (MDD).

4.7.4.1 Mechanism of action:

Vortioxetine is classified as a serotonin modulator and simulator (SMS) as it has a multimodal mechanism of action towards the serotonin neurotransmitter system whereby it simultaneously modulates one or more serotonin receptors and inhibits the reuptake of serotonin. More specifically, vortioxetine acts via the following biological mechanisms: as a serotonin reuptake inhibitor (SRI) through inhibition of the serotonin transporter, while also acting as a partial agonist of the 5-HT1B receptor, an agonist of 5-HT1A, and antagonist of the 5-HT3, 5-HT1D, and 5-HT7 receptors. (38,39)

4.7.4.2 Side-effects:

The most common adverse effects during clinical trials were nausea, diarrhea, and dry mouth. The FDA label includes a Blackbox warning for the following risks and complications: serotonin syndrome, especially when combined with other serotonergic agents; increased risk of abnormal bleeding, especially when combined with NSAIDs, aspirin, or other drugs that affect coagulation; activation of mania/hypomania; hyponatremia; and suicidal thoughts and behavior in children, adolescents, and young adults. (40)

4.7.5 Mianserin:

Mianserin is a tetracyclic antidepressant with therapeutic activity similar to amitriptyline used to treat depression and anxiety. (41)

4.7.5.1 Mechanism of action:

Mianserin's mechanism of therapeutic action is not well understood, although it apparently blocks alpha-adrenergic, histamine H1, and some types of serotonin receptors. (42)

4.7.5.2 Side-effects:

The main adverse effects of mianserin are drowsiness and dizziness. Significant cognitive impairment is more likely with mianserin than with SSRIs, and weight gain is a common problem. The most serious adverse effect of mianserin is a lowering of the white cell count, and fatal agranulocytosis has been reported. It is recommended that a blood count be obtained before starting mianserin treatment, and that the white cell count be monitored monthly for three months after treatment has started. (43)

4.7.6 Nefazodone:

4.7.6.1. Mechanism of action:

Nefazodone potently and selectively blocks postsynaptic serotonin (5-hydroxytryptamine; 5-HT) 5-HT2A receptors and moderately inhibits serotonin and noradrenalin (norepinephrine) reuptake. (44)

4.7.6.2 Side effects:

Nefazodone has a lower incidence of adverse anticholinergic, antihistaminergic and adrenergic effects than imipramine. Compared with SSRIs, nefazodone causes fewer activating symptoms, adverse gastrointestinal effects (nausea, diarrhea, anorexia) and adverse effects on sexual function, but is associated with more dizziness, dry mouth, constipation, visual disturbances and confusion. Available data also suggest that nefazodone is not associated with abnormal weight gain, seizures, priapism or significant sleep disruption, and appears to be relatively safe in overdosage. Nefazodone inhibits the cytochrome P450 3A4 isoenzyme and thus has the potential to interact with a number of drugs. (45) it is important to mention that cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. (46)

4.7.7 Opipramol:

Opipramol has chemical similarities with tricyclic antidepressants. Pharmacodynamic properties with absent reuptake inhibition of serotonin and noradrenaline and agonism at sigma receptors distinguish opipramol from tricyclics. Furthermore, antidepressive effects are smaller than the anxiolytic ones. (47)

4.7.7.1 Mechanism of action:

The mechanism of action of opipramol is currently not sufficiently understood. Agonistic effects at sigma receptors have been linked with therapeutic effects. (47)

4.7.7.2 Side-effects:

Mild disturbances of vigilance and anticholinergic adverse events are the predominant side effects. (47)

4.7.8 Trazodone:

Trazodone is triazolopyridine derivative from the serotonin receptor antagonists and reuptake inhibitors (SARIs) class of antidepressants. (48)

It has been used off-label for adjunct therapy in alcohol dependence, and off-label to treat anxiety and insomnia. It may also be used off-label to treat symptoms of dementia, Alzheimer's disease, schizophrenia, eating disorders, and fibromyalgia due to its effects on various neurotransmitter receptors. (49)

4.7.8.1 Mechanism of action:

The full spectrum of trazodone's mechanism of action is not fully known, which could explain its off-label uses. Trazodone works by inhibiting both serotonin transporter and serotonin type 2 receptors. Trazodone inhibits the reuptake of serotonin and blocks the histamine and alpha-1-adrenergic receptors. It also induces significant changes in 5-HT. The unique property of trazodone, where it simultaneously inhibits SERT, 5-HT2A, and 5-HT2C receptors, avoids the issue of sexual dysfunction, insomnia, and anxiety that commonly presents with SSRIs and SNRIs therapy, presynaptic receptor adrenoreceptors. (49)

4.7.8.2 Side-effects:

The primary adverse effects of trazodone include headaches, fatigue, dizziness, and drowsiness/somnolence. Other risks include anticholinergic effects (dry mouth),

orthostatic hypotension, QT prolongation, torsades, priapism, and an increase in suicidal thoughts. (49)

4.8. Serotonergic syndrome

Serotonergic syndrome is serious side-effect associated with the usage of antidepressants, but also with other classes of drug that affect serotonergic neurotransmission (like antimigraine drugs, some analgesics etc). The degree of symptoms can range from mild to severe, including a potentiality of death. Serotonin syndrome symptoms usually occur within several hours of taking a new drug or increasing the dose of a serotonergic drug. Signs and symptoms include: agitation or restlessness, insomnia, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, muscle rigidity, heavy sweating, diarrhea, headache, shivering but in severe cases high fever, heartbeat irregularity, seizures, unconsciousness. In severe cases, it can result in cardiovascular collapse, coma, and death. This syndrome can occur when a monoamine oxidase inhibitor is given with a serotonin reuptake inhibitor, pentazocine, or L-tryptophan. Therefore, it is mandatory to wait at least 2 weeks after stopping a serotonin reuptake inhibitor before starting a monoamine oxidase inhibitor, and at least 5 weeks if switching from fluoxetine, in view of this drug's long half-life. (50)

5. Conclusion:

There is no doubt about the effectiveness of antidepressant in the treatment of depression and anxiety. This group of medication have, and still, change millions of patients' lives for the better. Moreover, the benefits of a well-treated depression and/or anxiety are also social and economic. Nevertheless, anticipating, recognizing, and managing antidepressant side-effects are crucial for achieving remission in depression as well as preventing relapse and recurrence.

Educating patients about what to anticipate once starting therapy is as important as the therapy itself. While the side effects range from what seem to look like insignificant to the observer (dizziness, dry mouth, constipation etc.) to reducing quality of life (insomnia, sexual disfunction, wight gain etc.) and even life threatening (serotonergic syndrome); we, the treating physicians, must take them all with the most seriousness and address them all with outmost respect. Adjustment of the treatment to suit the patient as much as possible is of great importance. The concept of tailoring the treatment is getting sub-validation in people who are multi-drug patients which are much more likely to suffer from side-effects.

Researches have shown that the most effective way to treat depression is the combination of psychotherapy with pharmacotherapy, and that mild depressive and anxiety disorders should be managed with psychotherapy. (51)

To summarize, the benefits of a well-treated depression and/or anxiety patients are of grater benefit over the potential side effects. And yet, most people who are treated with antidepressants are prematurely cease their medical treatment without the consulting of their treating doctor or other medical professional.

It is of outmost important to educate the patients about the course of their illness and just as important, about the course of their treatment. The treating professionals should be as compassionate as possible to the patient complaints and encourage them to continue the treatment and change it if necessary so it would be more tolerable. In addition, the treating physician need to ensure that the patient is aware of being potentialy a chronically ill patient that sometimes needs a life-long therapy.

6.Acknowledgments:

Firstly, I would like to thank my mentor, Branka Aukst Margetic assist. prof. MD, PhD for her guidance, support, and expertise in writing this graduation paper.

I would like to thank my family for all the support and encouragement trough out my studies in the medical school of Zagreb.

And finally, I would like to thank my fiancée for her patience and understanding for the past six years.

7. References

1. Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. Int J Tryptophan Res. 2019; 12: 1178646919873925
2. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. Dialogues Clin Neurosci. 2008;10(4):409-18.
3. Agius M, Bonnici H. Antidepressant in use in clinical practice. Psych Danub. 2017; 29 (Suppl. 3): 667-71.
4. Fava M. The role of the serotonergic and noradrenergic nerutransmitters systems in the treatment of psychological and physical symptoms of depression. J Clin Psychiatry. 2003;64(Suppl 13):26-9.
5. Chand SP, Arif H. Depression. In: StatPearls. StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430847/
6. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chemistry. 1994;40:288–95. doi.org/10.1093/clinchem/40.2.288
7. Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). http://ghdx.healthdata.org/(approached 2nd January 2022)
8. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva, 2017.
9. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Benjet C, Bruffaerts R, Chiu WT, Florescu S, de Girolamo G, Gureje O, Haro JM, He Y, Hu C, Karam EG, Kawakami N, Lee S, Lund C, Kovess-Masfety V, Levinson D, Navarro-Mateu F, Pennell BE, Sampson NA, Scott KM, Tachimori H, Ten Have M, Viana MC, Williams DR, Wojtyniak BJ, Zarkov Z, Kessler RC, Chatterji S, Thornicroft G.Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. Psychol Med. 2018;48(9):1560-1571.

10. Kupfer DJ. Anxiety and DSM-5. Dialogues Clin Neurosci. 2015;17(3):245-246. doi:10.31887/DCNS.2015.17.3/dkupfer
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, ed. 5. Washington DC: APA Press; 2013.
12. Obsessive-compulsive disorder [Internet]. MedlinePlus. U.S. National Library of Medicine; 2021 [cited 2022Feb26]. Available from: https://medlineplus.gov/obsessivecompulsivedisorder.html
13. Maercker A, Brewin CR, Bryant RA, Cloitre M, van Ommeren M, Jones LM, Humayan A, Kagee A, Llosa AE, Rousseau C, Somasundaram DJ, Souza R, Suzuki Y, Weissbecker I, Wessely SC, First MB, Reed GM. Diagnosis and classification of disorders specifically associated with stress: proposals for ICD-11. World Psychiatry. 2013;12(3):198-206. doi: 10.1002/wps.20057.
14. Marvanova M, Gramith K. Role of antidepressants in the treatment of adults with anorexia nervosa. Ment Health Clin. 2018; 26;8(3):127-137. doi: 10.9740/mhc.2018.05.127.
15. Sansone RA, Sansone LA. Pain, pain, go away: antidepressants and pain management. Psychiatry (Edgmont). 2008;5(12):16-9.
16. Lopez-Munoz F, Alamo C. Monoaminergic neurotransmission: The history of the discovery of antidepressants from 1950s until today. Curr Pharm Des. 2009;15(14):1563–86.
17. Khawam EA, Laurencic G, Malone DA. Side effects of antidepressants: An overview. Cleveland Clin J Med. 2006;73:351-61
18. Finberg JPM, Rabey JM. Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. Front Pharmacol. 2016;7:340. doi: 10.3389/fphar.2016.00340.
19. Kleber RJ. Trauma and Public Mental Health: A Focused Review. Front Psychiatry. 2019;10:451. doi: 10.3389/fpsyt.2019.00451.
20. Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry. 2001; 3(1): 22–27. doi: 10.4088/pcc.v03n010

21. Brody DJ, Gu Q. Antidepressant use among adults: United States, 2015–2018. NCHS Data Brief, no 377. Hyattsville, MD: National Center for Health Statistics. 2020.
22. Whiskey E, Taylor D. A review of the adverse effects and safety of noradrenergic antidepressants. J Psychopharmacol. 2013;27(8):732-9. doi:10.1177/0269881113492027
23. Wang SM, Han C, Bahk WM, Lee SJ, Patkar AA, Prakash S. Masand PS, Chi-Un Pae CU. Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. Chonnam Med J. 2018;54(2):101–112. doi: 10.4068/cmj.2018.54.2.101
24. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, Zhong H, Nielsen SM, Hogg S, Mørk A, Stensbøl TB. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem. 2011; 12;54(9):3206-21. doi: 10.1021/jm101459g.
25. Wells BG, Gelenberg AJ. Chemistry, pharmacology, pharmacokinetics, adverse effects, and efficacy of the antidepressant maprotiline hydrochloride. Pharmacotherapy. 1981;1(2):121-39. doi:10.1002/j.1875-9114.1981.tb03559.
26. Hennings JM, Heel S, Lechner K, Uhr M, Dose T, Schaaf L, Holsboer F, Lucae S, Fulda S, Kloiberet S. Effect of mirtazapine on metabolism and energy substrate partitioning in healthy men. JCI Insight. 2019;4(1):e123786. doi:10.1172/jci.insight.123786
27. Toprak SK, Erdogan E, Azap OK. Mirtazapine-Induced Thrombocytopenia and Neutropenia. Turk J Hematol. 2012; 29(3): 297-298.
28. Dziedzicka-Wasylewska M, Rogoz Z, Skuza G, Dlaboga D, Maj J. Effect of repeated treatment with tianeptine and fluoxetine on central dopamine D(2) /D(3) receptors. Behav Pharmacol. 2002;13(2):127-38.
29. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol. 2007;151(6):737-48.

30. Gassaway MM, Rives ML, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a mu-opioid receptor agonist. Transl Psychiatry. 2014;4:e411. doi: 10.1038/tp.2014.30.
31. Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, Grinnell SG, Han J, Ansonoff MA, Pintar JE, Javitch JA, Sames D, Hen R. The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor. Neuropsychopharmacology. 2017;42(10):2052-2063. doi: 10.1038/npp.2017.60
32. Datla KP, Curzon G. Behavioural and neurochemical evidence for the decrease of brain extracellular 5-HT by the antidepressant drug tianeptine. Neuropharmacology. 1993;32(9):839-45.
33. Sonawalla S, Chakraborty N, Parikh R. Treatment of major depression and anxiety with the selective serotonin re-uptake enhancer tianeptine in the outpatient psychiatric care setting of India. J Indian Med Assoc. 2003;101(2):116-7, 124.
34. Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine. Mol Diag Ther 2001;15, 231–259.
35. Millan MJ, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. Psychopharmacology (Berl). 2005;177(4):448-58. doi: 10.1007/s00213-004-1962-z.
36. Wilde MI, Benfield P: Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. Drugs. 1995;49(3):411-39.
37. Racagni G, Riva MA, Popoli M. The interaction between the internal clock and antidepressant efficacy. Int Clin Psychopharmacol. 2007t;22 (Suppl 2):S9-S14. doi: 10.1097/01.yic.0000277957.75852.c7.
38. Smeraldi E, Delmonte D. Agomelatine in depression. Expert Opin Drug Saf. 2013;12(6):873-80. doi: 10.1517/14740338.2013.828690.
39. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, Zhong H, Nielsen SM, Hogg S, Mørk A, Stensbøl TB. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal

compound for the treatment of major depressive disorder. J Med Chem. 2011; 12;54(9):3206-21. doi: 10.1021/jm101459g.

40. Stenkrona P, Halldin C, Lundberg J. 5-HTT and 5-HT(1A) receptor occupancy of the novel substance vortioxetine (Lu AA21004). A PET study in control subjects. Eur Neuropsychopharmacol. 2013;23(10):1190-8. doi:10.1016/j.euroneuro.2013.01.002.
41. FDA Approved Drug Products: Trintellix (vortioxetine) tablets for oral use https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204447s021s022lbl.pdf (cited 22nd Jan 2022)
42. Petrie WM, Wilson WH, Ban TA, Guy W, Schaffer JD. Mianserin: determination of therapeutic dose range. Int Pharmacopsychiatry. 1980;15(2):111-7. doi: 10.1159/000468421. PMID: 7002830.
43. Rattay B, Benndorf RA. Drug-Induced Idiosyncratic Agranulocytosis - Infrequent but Dangerous. Front Pharmacol. 2021;12:727717. doi: 10.3389/fphar.2021.727717. PMID: 34483939; PMCID: PMC8414253.
44. Davis R, Whittington R, Bryson HM. Nefazodone. A review of its pharmacology and clinical efficacy in the management of major depression. Drugs. 1997;53(4):608-36. doi: 10.2165/00003495-199753040-00006.
45. de Boer TH, Nefkens F, van Helvoirt A, van Delft AM. Differences in modulation of noradrenergic and serotonergic transmission by the alpha-2 adrenoceptor antagonists, mirtazapine, mianserin and idazoxan. J Pharmacol Exp Ther. 1996 ;277(2):852-60
46. Cowen PJ, Psychopharmacology, Eds: Bellack AS, Hersen M, In: Comprehensive Clinical Psychology. New York: Elsevier; 1998. pp. 135-61.
47. Gahr M, Hiemke C, Connemann BJ. Update Opipramol [Update Opipramol]. Fortschr Neurol Psychiatr. 2017;85(3):139-145. doi: 10.1055/s-0043-100762.
48. Fagiolini A, Comandini A, Catena Dell'Osso M, Kasper S. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs. 2012;26(12):1033-49. doi: 10.1007/s40263-012-0010-5.

49. Shin JJ, Saadabadi A. Trazodone. 2021 Aug 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. https://www.ncbi.nlm.nih.gov/books/NBK470560/
50. Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin Syndrome: Pathophysiology, Clinical Features, Management, and Potential Future Directions. Int J Tryptophan Res. 2019;12:1178646919873925. doi: 10.1177/1178646919873925.
51. Unützer J, Park M. Strategies to improve the management of depression in primary care. Prim Care. 2012;39(2):415-431. doi:10.1016/j.pop.2012.03.010

8. Biography:

Harel Elia was born on March 30, 1993 in Israel. After his honorable discharge from the army and loosing several of his friends and comrades to depression during their military service, Harel understood the importance of mental health care and start his journey in Zagreb Medical School towards a medical career with intention to specialize psychiatry with a subspecialize in depression and PTSD.

As a medical student, Harel has completed visiting clinical electives in Psychiatry hospital Lev Hasharon in Israel.