REVIEW ARTICLE

CONTENTS

From efficacy to adversity: understanding the side effects of antidepressants – systematic review

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ABSTRACT

Aim: To investigate how and why antidepressant side effects occur, in order to use them effectively in clinical practice

Materials and Methods: We have studied modern literary sources on the topic of side effects of antidepressant and presented in the form of a literature review in this article. Electronic Scopus and Pubmed databases were searched for articles on the studied topic. The review included original articles, research, and official recommendations from medical associations.

Conclusions: Side effects of antidepressants can reduce treatment adherence and delay recovery. Therefore, it is extremely important to consider possible side effects when choosing a therapy. While there is no perfect antidepressant that works quickly and is completely free of side effects, newer antidepressants are safer, better tolerated, and associated with lower rates of treatment failure. Most side effects occur as a consequence of the basic mechanism of action of the drugs. Therefore, it is important to understand the neurobiology of side effects, their frequency and risks, ways to prevent them or use them to your advantage resources.

KEY WORDS: depression, anxiety disorder, tolerance, side effects, antidepressant

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INTRODUCTION

Antidepressants are among the most commonly prescribed medications. Studies show that the use of antidepressants has been increasing rapidly in recent decades. In some countries, the use of these medications has more than doubled over the past few years. One in ten US residents over the age of 12 takes antidepressants, and two-thirds of them do not have symptoms of depression [1-3]. Anxiety and stress-related disorders, phobias and eating disorders, functional disorders of the gastrointestinal tract and urination, numerous pain syndromes (including migraine, neuropathic and chronic pain), and sleep disorders are not a complete list of indications for the use of antidepressants. Despite the fact that these medications are the third most frequently prescribed and the fourth best-selling, there are some discussions and doubts about the effectiveness and clinical relevance of antidepressants in treating depression symptoms [2,4].

The well-known psychopharmacologist Stephen Stahl noted in this regard: "Whatever the reason for the controversy over efficacy in research, even a short time spent in clinical practice convinces us that antidepressants are powerful therapeutic agents for many patients" [5]. Large-scale meta-analyses in recent years agree with this view and show that antidepressants are more effective than placebo, and that the lack of clinical effect is more likely to be due to imperfect patient selection and poor adherence to treatment [6].

Although modern antidepressants are quite effective and well tolerated by patients, the lack of compliance and the frequency of premature discontinuation of treatment are worrying. Up to 70% of patients have problems with treatment adherence, one third will stop taking antidepressants within the first month and almost half within the first three months [7]. In general, treatment discontinuation is more likely with tricyclic antidepressants (as high as 44%) and serotonin-norepinephrine reuptake inhibitors, although in studies of safer selective serotonin reuptake inhibitors, almost one in four patients discontinue treatment [6].

Despite the emergence of newer, more selective and pharmacologically engineered drugs, antidepressants are still far from perfect. In particular, it takes at least two weeks of use to achieve the desired effects, and side effects occur almost immediately. This feature contributes to a loss of compliance, leading to premature discontinuation of treatment, which in turn makes it

impossible to achieve a clinical effect. It is in the physician's power to anticipate adverse events, convince the patient that they are benign or temporary, and thereby improve adherence to treatment.

The purpose of this article is to familiarize the reader with the current understanding of how and why antidepressant side effects occur, in order to use them effectively in clinical practice. Most studies consider side effects of drugs from a clinical or statistical point of view, but we will try to consider the neurobiological aspects of these effects to better understand the reasons for their occurrence and thus the possibility of preventing, reducing or even using them to the benefit of the patient.

AIM

To investigate how and why antidepressant side effects occur, in order to use them effectively in clinical practice

MATERIALS AND METHODS

We have studied modern literary sources on the topic of side effects of antidepressant. The studied material is summarized and presented in the form of a literature review in this article. The search for literary sources was carried out in two main scientific databases: Scopus and PubMed. The review included original articles, research, and official recommendations from medical associations.

REVIEW AND DISCUSSION

1. ANTIDEPRESSANTS: THE EFFECT AND ITS SHADOWS

The general pathway of antidepressant action can be represented as blocking transporters or reuptake of serotonin, norepinephrine and/or dopamine, which leads to an increase in their levels in the synaptic cleft and prolongation of their effect on postsynaptic terminals. In the 50s of the last century, the antidepressant effect of iproniazide and the "father of tricyclic antidepressants", imipramine, was discovered [8]. In the 1960s, Glowinski and Axelrod showed that these drugs could inhibit presynaptic norepinephrine reuptake [9]. Since then, the "monoamine hypothesis of depression" and the synthesis of molecules that affect the level of certain monoamines have been developing. The synthesis and approval of fluoxetine in 1987 marked the beginning of the explosion of a new generation of antidepressants with selective serotonin reuptake inhibition. The absence of significant effects on other receptors and electrolyte channels, unlike the first generation, significantly improved the safety profile and tolerability of the new drugs.

The monoamine hypothesis in its original form is significantly simplified, as an important factor is not just an increase in the level of certain transmitters, but also the adaptation of the number and sensitivity of receptors due to gene expression, followed by deeper neuroplastic changes. These mechanisms explain the aforementioned feature of antidepressants: mediator levels increase relatively quickly and immediately cause side effects, as it takes time for receptor regulation, gene expression, and neural circuitry to achieve the desired effects [5].

In one of the first large-scale meta-analyses of antidepressant tolerability, which included a review of 84 clinical trials, the authors identified more than fifteen adverse effects and grouped them by frequency of occurrence [10] (Table 1).

Headache, tremor, and hypotension were the most nonspecific and occurred equally frequently regardless of the drug being taken. The second group of side effects was more common among patients taking tricyclic antidepressants: dry mouth, constipation, diplopia, dizziness and palpitations. Symptoms such as nausea, loss of appetite, anxiety, anxiety and insomnia were more common with selective serotonin reuptake inhibitors.

Most side effects can be logically explained by the chemical structure of the drugs and their effect on certain receptors (Fig. 1, Table 2).

Tricyclic antidepressants have the widest range of side effects due to their multimodal effects on cellular structures (Fig. 1). The blockade of M_{1-} acetylcholine receptors causes dry mouth, constipation and urinary retention, diplopia, and, in part, sedation. A powerful, rapid sedative effect, weight gain, and prolongation of the QT interval are the consequences of blocking H_1 -histamine receptors. Effects on voltage-gated sodium channels cause cardiotoxicity, cardiac dysrhythmias, or even death in case of overdose. Orthostatic hypotension is caused by blockade of α -adrenoceptors.

Interestingly, paroxetine, the only SSRI that blocks muscarinic receptors (M_3), has a more pronounced sedative effect in its class and a greater tendency to increase weight. On the other hand, the R-enantiomer of citalopram affects H_1 -histamine receptors, so in high doses it is more dangerous in terms of QT prolongation compared to other SSRIs. The isolation of the S-enantiomer into a separate drug (escitalopram) weakens the antihistamine effect, making this molecule a "perfectly selective" serotonin reuptake inhibitor [5].

No matter how selective modern antidepressants are, it is stated that 80% of patients experience at

Table 1. The most frequent side effects of using "monoamine" antidepressants ("atypical" antidepressants are discussed in the text)

Class of antidepressant	Mechanism of action	Side effects
Tricycle (TCA)	Blockade of serotonin, norepinephrine, H_1 -histamine receptors, α_1 -adrenergic receptors, M_1 -cholinergic receptors, voltage-gated Na^+ channels	Cardiotoxicity, dry mouth, constipation and urinary retention, diplopia, orthostatic hypotension, drowsiness and sedation
Serotonin reuptake inhibitors and norepinephrine (SNRI)	Blockade of serotonin and norepinephrine reuptake	Nausea, sexual dysfunction, increased sweating, arterial hypertension
Selective serotonin reuptake inhibitors (SSRIs)	Serotonin reuptake blockade	Nausea, loss of appetite, sexual dysfunction

Table 2. Side effects of antidepressants depending on the mechanism of action

Mechanism of action	Clinical effect
Serotonin reuptake blockade	Nausea, diarrhea Loss of appetite at the beginning of treatment and weight gain later Decreased libido, anorgasmia Sedation, insomnia, increased anxiety Serotonin syndrome
Blockade of the norepinephrine transporter	Increased blood pressure Anxiety and tremors Tachycardia Increased sweating
Dopamine reuptake blockade	Psychomotor agitation, akathisia Provoking psychosis Parkinsonism
H1 histamine receptor blockade	Drowsiness and easier falling asleep Sedation and anxiolytic effect Increased risk of falls in old age Weight gain
Blockade of muscarinic acetylcholine receptors	The duality of the gaze Sedation, memory and cognitive impairment Dry mouth, constipation Sinus tachycardia Urinary retention Exacerbation of angle-closure glaucoma
Blockade of α1 adrenergic receptors	Orthostatic (postural) hypotension and dizziness Reflex tachycardia Strengthening the effect of antihypertensive drugs

Table 3. Monoamine receptors regulating sexual function (adapted from [26])

System	Receptor	Effect on sexual function
Dopamine	D /D_{12}	Activation
Serotonin	5-NT 1A	Activation (indirect effect through activation of D2 receptors)
	5-NT 1B/1D	Suppresses
	5-NT 2A	Suppresses
	5-NT 2C	Suppresses

least one side effect, and almost every second patient experiences several side effects at the same time. The most frequent side effects of serotonin reuptake inhibitors are, so to speak, a shadow of the main effect. An increase in serotonin levels leads to activation of serotonergic neuronal receptors, a gradual increase in neurotransmission of mediators by these neurons leads to an antidepressant or anxiolytic effect, but activation of "undesirable" receptor subtypes by serotonin causes side effects [11-12] (Fig. 2).

The mechanism of action of antidepressants of other groups is mostly associated not only with the blockade of serotonin and/or norepinephrine transporters, but also with the direct effect on the receptors by the molecule itself. For example, trazodone, in addition to blocking serotonin reuptake, directly blocks 1A/2C sero-

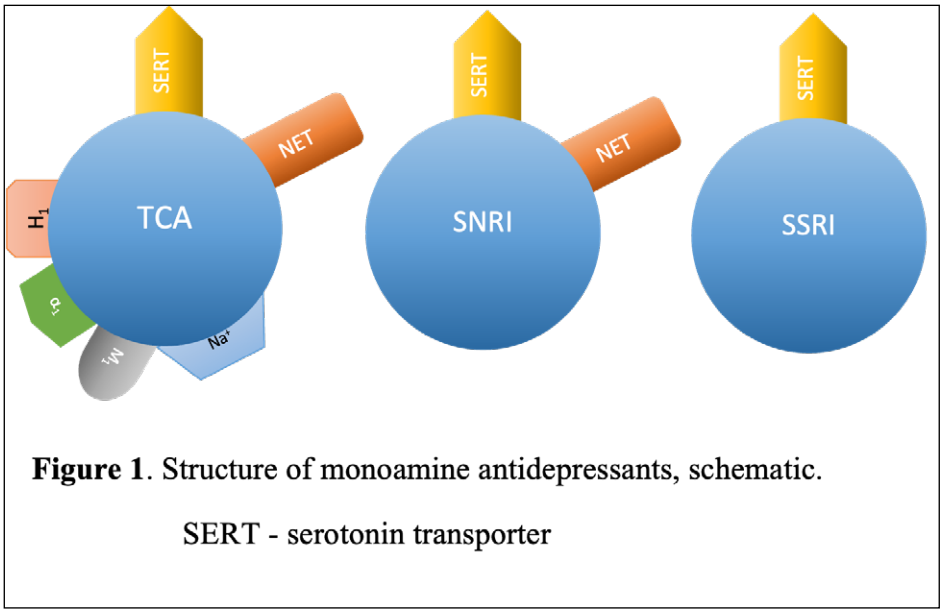

Figure 1. Structure of monoamine antidepressants, schematic.

SERT - serotonin transporter

Fig. 1. Structure of monoamine antidepressants, schematic. SERT - serotonin transporter. NET - norepinephrine transporter.

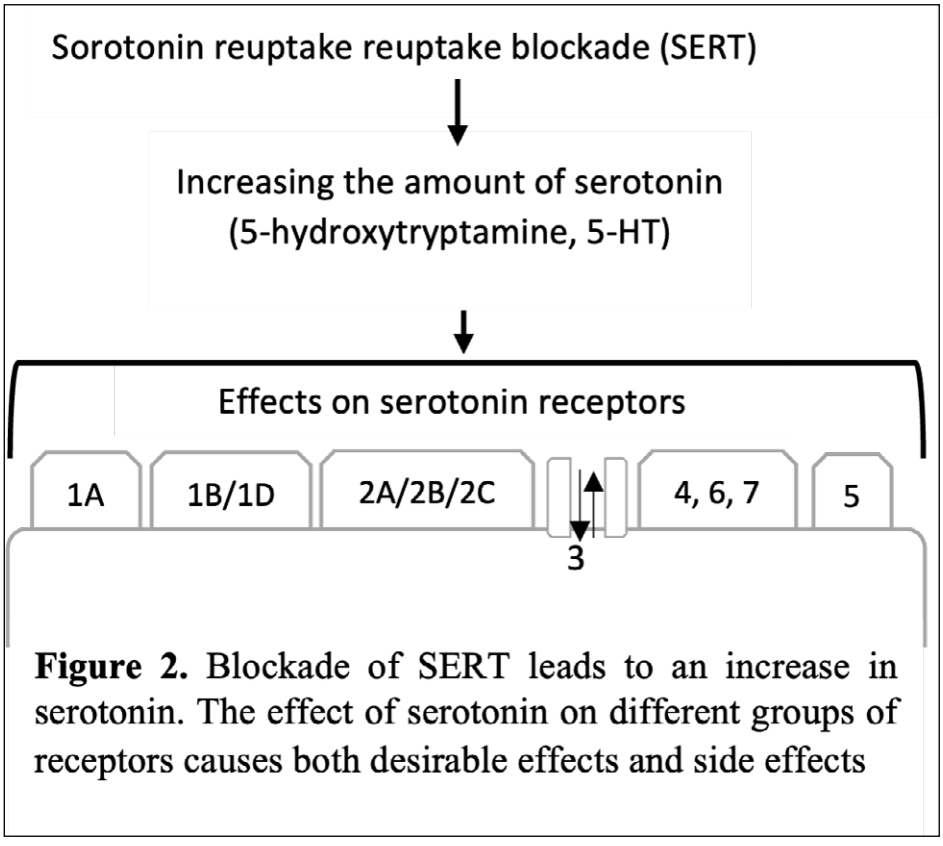

Figure 2. Blockade of SERT leads to an increase in serotonin. The effect of serotonin on different groups of receptors causes both desirable effects and side effects

Fig. 2. Blockade of SERT leads to an increase in serotonin. The effect of serotonin on different groups of receptors causes both desirable effects and side effects.

tonin receptors, as well as α_1 -adreno- and H_1 -histamine receptors, which is the cause of, among other things, hypnotic and anxiolytic effects. Agomelatine is a melatonin receptor agonist and a serotonin receptor antagonist of type 2A/2C, which determines a good hypnotic effect and a mild antidepressant effect. Mianserin and mirtazapine do not affect monoamine transporters at all, but block α_2 and H_1 receptors: the first mechanism provokes the release of norepinephrine and stimulation of serotonergic neurons, the second is already known to improve sleep and reduce anxiety [13].

The effects of these "atypical" antidepressants and the possibilities of using their side effects to your advantage will be discussed in more detail below. We will start with the side effects that are the most common causes of treatment failure and loss of compliance

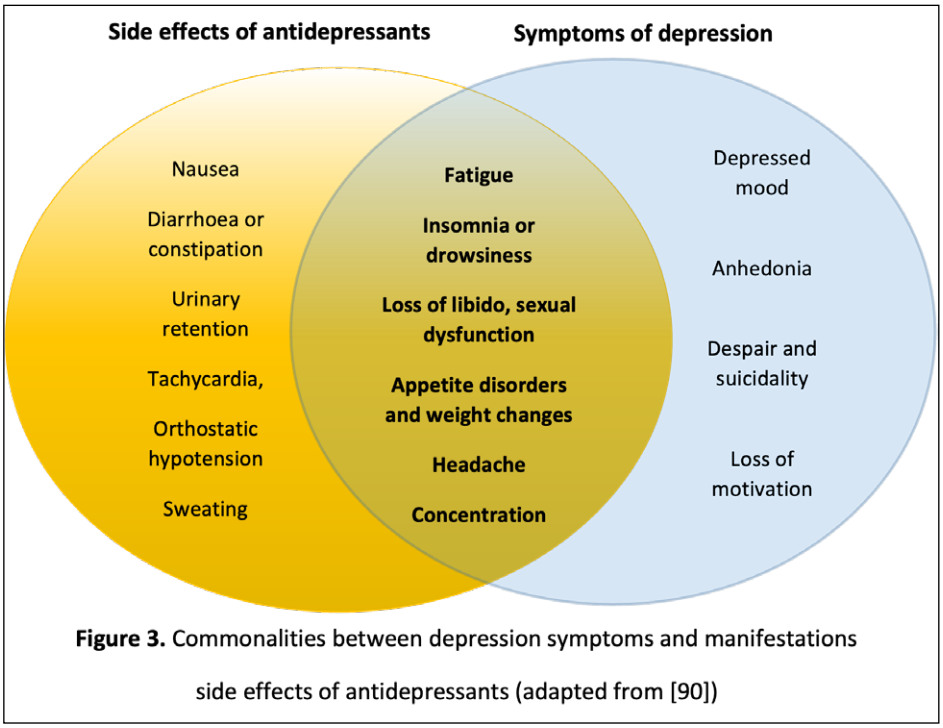

Figure 3. Commonalities between depression symptoms and manifestations side effects of antidepressants (adapted from [90])

Fig. 3. Commonalities between depression symptoms and manifestations side effects of antidepressants (adapted from [40]).

Table 4. Frequency of sexual dysfunction during treatment with different antidepressants (adapted from [29])

	Summary frequency of sexual dysfunction		
	< 30 %	**10-30%**	**> 30 %**
Antidepressant	Agomelatine Mirtazapine Bupropion	Escitalopram Duloxetine Venlafaxine	Paroxetine Sertraline Fluoxetine Fluvoxamine

GASTROINTESTINAL EFFECTS AND NAUSEA

Unpleasant gastrointestinal symptoms are among the most common complaints when taking antidepressants, especially at the beginning of treatment (occurring in more than a third of patients).

Dry mouth and constipation are characteristic of all tricyclic antidepressants and high doses of paroxetine, which is a consequence of a decrease in secretion and slowing of peristalsis (M-cholinergic receptor blockade). The most pronounced anticholinergic effects are inherent in amitriptyline, imipramine, and doxepin, with somewhat lesser effects in nortriptyline and desipramine [14,15].

Nausea is one of the first unwanted symptoms of increased serotonin levels and is common during the initial period of treatment with all selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors. Activation of serotonin receptors of the third type (5-HT3) both in the central nervous system (postrema area) and in the periphery (parasympathetic gut terminals) is a key pathophysiological mechanism of nausea and vomiting. These effects are temporary and dose-dependent: gradual desensitization of 5-HT3 receptors (up to 2 weeks) reduces the negative gastrointestinal effects of serotonin, and their blockade is used, for example, to relieve nausea and vomiting in the postoperative period or during chemotherapy [16].

Sertraline, fluvoxamine, and duloxetine cause nausea and transient diarrhea somewhat more frequently than other antidepressants [17]. Accordingly, a simple recommendation to reduce the dose or take the medication with food is usually sufficient to reduce these side effects.

EFFECTS ON APPETITE/EATING AND WEIGHT

Transient loss of appetite is relatively common at the beginning of treatment with serotonergic medications, although it is not as threatening a side effect as weight gain or metabolic syndrome. Along with nausea, weight gain is one of the most common reasons for discontinuing antidepressant treatment [18]. Increased appetite and weight gain with long-term antidepressant use is

associated with blockade of 5-HT2C and H_1 receptors, while their activation (as well as 5-HT1A, 1B) leads to loss of appetite.

Studies show that weight gain with prolonged use of SSRIs and SSRIs (6-36 months) is observed in half of patients, with the vast majority of patients showing an increase of more than 7% compared to the start of therapy. Escitalopram, paroxetine, sertraline, duloxetine, venlafaxine, and mirtazapine showed the most significant effect, and fluoxetine showed the least [19]. Independent risk factors are low body mass index and a family history of overweight.

There is evidence that antidepressants can provoke the development of metabolic syndrome or diabetes mellitus [20]. While monitoring of metabolic changes has become routine with modern antipsychotics, it is often ignored for antidepressants. Another negative fact from the point of view of clinical management is that weight gain may be delayed. On the other hand, weight gain at the beginning of antidepressant treatment is a reliable predictor of further weight gain [21].

As for other classes of antidepressants, blockade of the H_1 receptor is a powerful additional mechanism for increasing appetite and weight gain, which is typical, for example, for tricyclic antidepressants [21].

The above mechanisms can be used to correct loss of appetite or to increase body weight. Mirtazapine, as a blocker of 5-HT2C and H_1 receptors, is the drug of choice in this case [22]. In children and adolescents with eating disorders, fluoxetine (direct 5-HT2C antagonism, but without effects on H_1) is often recommended due to the availability of a larger evidence base and the absence of antihistamine side effects [23].

SEXUAL DYSFUNCTION

Reduced libido, erectile dysfunction, and delayed ejaculation are common side effects of antidepressants, especially serotonin reuptake inhibitors. Deterioration in quality of life and treatment refusal are much more common among patients with adverse sexual dysfunction [24]. It is worth noting that loss of libido is also one of the characteristic symptoms of depressive disorder, so it is often ignored by many clinicians and is not associated with treatment [25].

In order to understand the cause and ways of correcting sexual disorders when using monoamine antidepressants, it is worthwhile to understand the basics of physiology and neuropharmacology of sexual function (Table 3).

Sexual desire is a complex phenomenon that is controlled by hormones (testosterone and estrogens) and neurotransmitters, mainly dopamine. It is dopamine that increases sexual desire by activating the mesocorticolimbic and tuberoinfundibular pathways. Selective serotonin reuptake inhibitors suppress libido by blocking dopaminergic neurons in the ventral tire area, which give rise to the mesocorticolimbic pathway [27].

Sexual arousal is impossible without the activation of the autonomic nervous system, the release of acetylcholine and nitric oxide (NO) as vasodilatory agents that stimulate blood flow to the genitals. Elevated serotonin levels and anticholinergic effects block NO release, smooth muscle relaxation, and, consequently, arousal [5,27].

Orgasm is caused by activation of descending spinal noradrenergic pathways and sympathetic innervation of the genitals. Dopamine also enhances orgasm. In contrast, activation of descending serotonergic pathways, presumably through 5-HT 1B/2A/2C receptors, suppresses orgasm and slows ejaculation. It is worth noting that serotonin 1A receptor agonists do not have a negative impact on sexual function, as they are often also D2 dopamine receptor agonists.

The overall incidence of sexual dysfunction varies considerably, depending on study design, sponsorship or conflict of interest, control methods (self-report or standardized questionnaires), etc. . Interestingly, the incidence of anorgasmia as a side effect of antidepressants is almost the same in men and women [28].

To understand the general trends, it is convenient to use the adapted data from Kennedy et al. (2007) (Table 4).

Many prospective multicenter studies have confirmed that paroxetine is the most commonly used medication for sexual dysfunction, followed by other SSRIs, duloxetine and venlafaxine, and even less commonly by bupropion and mirtazapine. In the study by Serretti and Chiesa (2009), agomelatine, bupropion, and mirtazapine showed a level of sexual dysfunction comparable to placebo [30].

Trazodone stands out significantly in the issue of sexual dysfunction, as it can be used specifically for its correction. Antagonism of the 5-HT 2A/2C receptor (see Table 3) improves libido and arousal, while adrenolytic properties (α1-antagonism) improve erectile function due to smooth muscle relaxation and improved blood flow [31]. In addition to trazodone, bupropion (inhibits norepinephrine and dopamine transporters), sildenafil (potentiates the peripheral action of NO), amantadine (dopamine receptor agonist), or a change of therapy to an antidepressant with a lower incidence of relevant side effects (bupropion, mirtazapine) are also often used to correct sexual dysfunction provoked by antidepressants. The choice of an "antidote" usually depends on the antidepressant that provoked the side effect, the

immediate type of dysfunction, the patient's preferences, and the clinician's clinical experience.

In some cases, antidepressants can be used as symptomatic therapy for sexual dysfunction in patients without depressive disorder or other indications for these drugs. Activation of 5-HT2C and stimulation of 5-HT1A receptors is stated to be one of the causes of anorgasmia and prolonged ejaculation time in patients taking serotonergic antidepressants. This side effect is used as a therapeutic one, in particular, for premature ejaculation: SSRIs (paroxetine, sertraline), duloxetine, or even clomipramine (as the most serotonergic TCA) are frequent off-label prescriptions in such cases [32].

COMMON CNS SIDE EFFECTS INCLUDE DROWSINESS OR INSOMNIA, ANXIETY, AGITATION, OR, CONVERSELY, SEDATION

As already mentioned, blockade of H_1 histamine and muscarinic acetylcholine receptors (Table 2) causes sedation, drowsiness and facilitates sleep when using many antidepressants, in particular tricyclics. Doxepin has the most pronounced antihistamine effect among all members of the class. Among SSRIs, paroxetine has a slightly greater sedative effect (anticholinergic effect). Other antidepressants that are often used in insomnia and have a powerful "hypnotic" effect are characterized by their effect on H_1 receptors: mianserin, mirtazapine and trazodone. [5]

Agomelatine is somewhat different in terms of its mechanism of hypnotic effect. Agonism of MT_1 and MT_2 melatonin receptors, as well as blockade of 5-HT2C receptors in the hypothalamic suprachiasmal nucleus (which is a brain pacemaker) leads to normalization of the sleep-wake cycle without severe daytime sleepiness and other side effects inherent in antihistamine antidepressants [33].

Insomnia and increased anxiety are fairly common complaints at the beginning of the use of selective serotonin reuptake inhibitors. These effects are mostly temporary and dose-dependent. [34]

CARDIOVASCULAR COMPLICATIONS, BLOOD PRESSURE AND BLEEDING RISK

The risks of antidepressant use in relation to the cardiovascular system have been well known since the widespread use of tricyclics. Of course, the effect on electrolyte channels, adrenergic and cholinergic systems cannot be absolutely safe, and such threatening complications as Q-T interval prolongation and arrhythmias have become a significant limitation to the use of "old generation" antidepressants. Blockade of α-adrenergic receptors with tricyclics often provokes orthostatic hypotension and reflex tachycardia (also typical of trazodone).

Modern selective serotonin reuptake inhibitors are considered safer, although cases of the same side effects have been reported, mostly with high doses. There is a recommendation to perform an ECG in all patients before using antidepressants. Particular attention is paid to elderly patients, as well as during titration and dose increases. [35]

Hypertension, potentiation of pressor effects, and provocation of hypertensive crises have been described as side effects of serotonin and norepinephrine reuptake inhibitors. Venlafaxine has potentially the most unfavorable profile in this group of effects, requires constant blood pressure monitoring and should be used with caution in patients with hypertension [36].

Over the past few decades, there have been reports of an increased risk of bleeding with selective serotonin reuptake inhibitors [37]. A study of the United Kingdom general practice database showed that antidepressants with serotonergic effects significantly increase the risk of gastrointestinal bleeding. The highest risk was observed with sertraline, escitalopram and venlafaxine, which was at least 2 times higher than in the control group. Concomitant use of NSAIDs or steroids doubles the risk, while the use of antacids or proton pump inhibitors has a protective effect. According to the results of this study, the risk of upper gastrointestinal bleeding among patients taking SSRIs is: 1 case per 2000 patients treated, while concomitant use of NSAIDs increases this rate to 1 case per 250 patients, and low-dose aspirin - 1 case per 500 [37].

INSTEAD OF CONCLUSIONS: BEYOND NEUROBIOLOGY

The effect on the serotonergic system, norepinephrine and dopamine, on numerous receptors in the nervous system and beyond determines both the positive therapeutic effect of antidepressants and their side effects. Even the most selective serotonin reuptake inhibitors have numerous side effects that are directly related to their underlying mechanism of action. Perhaps the "antidepressant of the future" should only affect certain receptors without a general increase in mediator levels or impact on "side targets," but even in this seemingly ideal case, in such a holistic system as the brain, imbalances in neural circuits and pathways appear, which inevitably lead to undesirable consequences [38].

Unfortunately, the level of evidence and the ability to translate "direct" research findings into practice is limited by several factors. First of all, many symptoms of the underlying

disorder (e.g. depression) and clinical manifestations of side effects are very similar [39]. Sometimes it is difficult to distinguish between patient complaints and classify them as side effects or symptoms that existed before treatment (Fig. 3).

One of the most unpleasant phenomena in pharmacotherapy is the nocebo effect [40]. Negative expectations of the patient regarding treatment, often based on previous experience, as well as somatic symptoms mimicking side effects, general level of anxiety, somatisation and neuroticism - all these factors significantly affect the success or, in this case, the failure of therapy.

It is important to remember that prescribing a drug, especially one from the psychotropic group, is not treatment, but only a part of the therapeutic relationship between a doctor and a patient. Each of these parties has their own vision of the disease, expectations of success or failure, fear of side effects or confidence in their absence... In these circumstances, not only psychopharmacology or neurobiology, but also the individual psychology of the patient is a crucial factor, because, first of all, the quality of the relationship and adherence to treatment determines its ultimate success.

CONCLUSIONS

Side effects of antidepressants can reduce treatment adherence and delay recovery. Therefore, it is extremely important to consider possible side effects when choosing a therapy. While there is no perfect antidepressant that works quickly and is completely free of side effects, newer antidepressants are safer, better tolerated, and associated with lower rates of treatment failure. Most side effects occur as a consequence of the basic mechanism of action of the drugs. Therefore, it is important to understand the neurobiology of side effects, their frequency and risks, ways to prevent them or use them to your advantage.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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