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Article

Role of Pharmacokinetics and Pharmacogenetics of Antidepressant-Induced Prolongation of the QT Interval and Torsade de Pointes in Patients with Mental Disorders

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Abstract: Antidepressants (ADs) include drugs of various pharmacological groups, which are mainly used for the treatment of mental disorders (major depressive disorder, obsessive-compulsive disorder, social phobia, panic disorder, generalized anxiety disorder, post-traumatic stress disorder), chronic pain and addiction diseases. Chronic use of ADs can lead to the development of cardiotoxic adverse drug reactions (ADRs). The most important cardiotoxic AD-induced ADRs are prolongation of the QT interval, ventricular tachycardia of the "pirouette" type (Torsades de Pointes - TdP). This narrative review analyzes and summarizes the results of studies on pharmacokinecis and pharmacogenetics of ADs on QT interval prolongation and updates physicians' knowledge of the risk of developing AD-induced TdP in patients with psychiatric disorders.

Keywords: *antidepressant; safety; adverse drug reaction; QT interval; long QT syndrome; risk factor; anti-depressant-induced repolarization disorder; Torsades de Pointes; sudden death syndrome; treatment.*

Introduction

Antidepressants (ADs, known as thymoanaleptics) are psychotropic drugs that have a predominant effect on pathologically low mood (depressive affect) that do not cause an increase in mood in healthy individuals [1]. This is a class of drugs used to treat major depressive disorder, obsessive-compulsive disorder, social phobia, panic disorder, generalized anxiety disorder, post-traumatic stress disorder [2], chronic pain, and addiction diseases [3]. ADs are the most frequently prescribed drugs for patients aged 12 to 44 years. They are the third most prescribed drugs for patients of all ages [4] and the first most frequently used among all psychotropic drugs [5, 6].

The main stages in the treatment of mental disorders requiring the appointment of ADs are stopping, stabilizing and anti-relapse. The stage of relief of symptoms of a depressive disorder lasts an average of 6-8 weeks [7]. The stabilizing stage lasts from 4 to 9 months [7]. Continuous long-term use of ADs at a standard dose is recommended in the case of frequent recurrence of depressive disorders and their significant severity, which proved to be effective during the relief phase of treatment. The anti-relapse (preventive) stage can sometimes last for years [7]. More than 60% of patients with depressive disorders have been taking ADs for more than 2 years, and 14% for more than 10 years [8]. However, chronic use of ADs can lead to the development of adverse reactions (ADRs). The World Health Organization (WHO) defines ADRs as any unintended and harmful effect on the human body under the conditions of using a drug at a standard dose [9]. The results of numerous studies indicate that AD-induced ADRs are recorded in 2.9% - 16.6% of hospitalized patients [10].

The traditional classification of ADRs includes two main types: type A reactions (dose-dependent and predictable) (non-immunological, commonly referred to as intolerance) and type B reactions (unpredictable and dose-independent) (immunological, allergic) [11]. Most ADRs (up to 90%) are type A [12]. Importantly, AD-induced ADRs can lead to the development of a serious adverse event, which is any unfavorable clinical manifestation, which, regardless of the dose of the ADs, leads to one of the following conditions: death; high danger to life; requires hospitalization or its extension; leads to a persistent decrease or loss of ability to work (disability); causes congenital anomalies and malformations before conception and in pregnant women; requires surgery or other medical intervention [13]. One of the important cardiotoxic AD-induced ADR is drug-induced prolongation of the QT interval, which can lead to a serious adverse event - ventricular tachycardia of the "pirouette" type (Torsades de Pointes (TdP)) and sudden death syndrome (SDS) [14, 15]. The increase in the number of new published case re-ports of AD-induced QT and/or TdP prolongation, experimental and clinical studies, and the registration of new generation ADs explain the need to update the knowledge of practitioners (primarily, psychiatrists, neurologists and general practitioners) about this problem of psychopharmacotherapy.

The purpose of this narrative review is to analyze the results of studies on pharmacokinetic and pharmacogenetics of ADs on QT interval prolongation and updates physicians' knowledge of the risk of developing AD-induced TdP in patients with psychiatric disorders.

Materials and Methods

Search Strategies

The keywords “antidepressant”, “safety”, “adverse drug reaction”, “QT interval”, “long QT syndrome”, “risk factor”, “antidepressant-induced repolarization disorder”, “Torsades de Pointes”, “sudden death syndrome”, “treatment” and their combinations were used to search for full-text articles in bibliographic databases: PubMed, Springer, Wiley Online Library, Taylor & Francis Online, APA PsycInfo, CORE, Science Direct, Google Scholar, eLIBRARY.RU.

Placebo-controlled studies, crossover studies, case-control studies, case studies, systematic reviews, meta-analyses and Cochrane reviews were analyzed. Articles published from July 2013 to June 2023 were analyzed. The last search date was 30 June 2023.

Data analyzed were preliminarily identified from identified studies by title and abstract, or from the entire publication if the title and abstract did not provide sufficient information about the type of study.

Duplicate articles have been excluded from this narrative review.

Several papers published prior to this period were also included in the review due to their high scientific value or if they were of historical interest. We analyzed 53 studies in this narrative review.

Results

Mechanisms of Antidepressant-Induced QT Interval and Torsades de Pointes

The QT interval is the time from the onset of ventricular depolarization to the end of ventricular repolarization. The underlying physiological processes are the result of the flow of sodium, potassium and calcium ions through specific receptors located in the cell membrane and endoplasmic reticulum. Sodium ion channels are mainly responsible for depolarization. However, a late sodium current promotes repolarization. Calcium ion channels are important in maintaining the plateau phase of the action potential, and potassium ion channels play an important role in repolarization. Abnormalities of these channels can have a strong influence on the action potential of cardiomyocytes [16]. For example, drug-induced potassium channel disruption can prolong repolarization, resulting in QT interval prolongation [17, 18, 19].

The duration of the QT interval depends on the heart rate (HR). Deceleration of heart rate leads to prolongation of the QT interval and vice versa [15]. In this regard, for a more accurate analysis of the QT interval, formulas for calculating the "corrected QT interval" (QTc) were proposed [17]. The formula proposed by Bazett is most often used in clinical practice, although it is associated with potential overcorrection at high HR and undercorrection at lower HR [20, 21]. The use of Bazett formula is justified at HR from 60 to 100 bpm [15]. Other formulas in the analysis of the duration of the QT interval may be more accurate [20]. The use of the Frederick's formula is more correct when the HR is less than 60 bpm and more than 100 bpm [15]. Framingham and Hodges formulas should be used when calculating QTc in patients with atrial fibrillation [15].

The U.S. Food and Drug Administration (FDA) recommends that the QTc interval be calculated primarily using the Frederick formula, as well as other formulas, except for the Bazett formula, which, in their opinion, is the worst for this purpose [22, 23] (Figure 1).

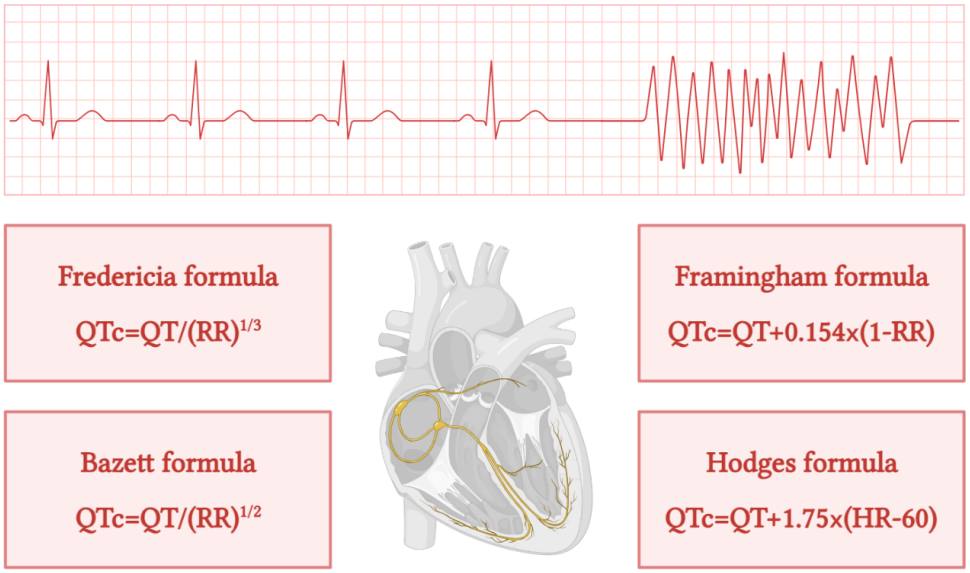

Figure 1. Formulas for calculating the corrected QT interval.

Normal QTc is 340–450 msec for women and 340–430 msec for men [24]. It should be noted that the duration of the QTc interval in women decreases with age [25]. There is a hypothesis that the activity of the ion channels of the heart changes under the influence of sex hormones, which, in turn, affects the QT interval [26]. Thus, differences in the QTc interval prolongation between men and women decrease with age [17] as estrogen levels decline in postmenopausal women.

Prolongation of the QTc interval in patients with depressive disorders may be the result of a comorbid hereditary long QTc syndrome or acquired conditions such as drug-induced prolongation of the QTc interval [17, 27, 28] or alcohol-induced prolongation of the QT interval [17, 27, 28, 29]. Various genetic mutations and polymorphisms lead to congenital long QTc syndrome (eg, Romano-Ward syndrome, Jervell-Lange-Nielsen syndrome), which occurs in about 1 in 2,000 newborns [17, 30, 31]. Acquired prolongation of the QTc interval is more common than the congenital form and is often the result of structural heart disease (eg, myocardial infarction, heart failure, left ventricular hypertrophy) and drugs that prolong the QTc interval [14, 17]. The mechanisms of AD-induced QTc interval prolongation continue to be actively studied, but are still not fully known.

Blockade of the voltage-dependent sodium channels on the membrane of cardiomyocytes by ADs is considered as one of such mechanisms [32]. Voltage-dependent sodium channels are critical determinants of the electrophysiological properties of the heart. The inward (depolarizing) sodium current (INa) is responsible for the rapid depolarization of the initial action potential and is a key factor in cardiac conduction velocity. Blockade of sodium channels slows down the depolarization of the heart and prolongs the QTc interval. Among the nine functional α-subunits of sodium channel isoforms (Nav1.1–Nav1.9), the cardiac subunit Nav1.5 is involved in action potential propagation in the myocardium. Its dysfunction can cause prolongation of the QT interval. Therefore, the Nav1.5 subunit is an important target for pro- and antiarrhythmic drugs, including ADs [33].

Another proposed mechanism for AD-induced prolongation of the QTc interval is inhibition of fast, delayed-rectifier potassium current (IKr) due to blockade of hERG potassium channels [33, 34]. The hERG channels appear to have a large porous cavity, unlike the other six transmembrane domains of potassium channels, and contain aromatic amino acid residues in the S6 region of the channel, making the hERG channel highly susceptible to drug interactions [35].

Finally, the cardiotoxicity of some ADs may result from their interaction with several cardiac target molecules [33]. However, this mechanism of AD-induced QT prolongation continues to be debated.

According to one guideline, AD-induced prolongation of the QT interval is defined as a QTc of 500 msec or more, or an increase in the QTc interval of 60 msec or more compared with the initial interval before treatment [34]. According to other guidelines, ADs that prolong the QTc interval by more than 20 msec from baseline [17, 36] and even 10 msec from baseline should be of concern [22, 37, 38].

AD-induced prolongation of the QTc interval can be accompanied by arrhythmogenic post-depolarization and lead to the development of a condition known as TdP. This is a potentially life-threatening form of polymorphic ventricular tachycardia [24, 39-41], which is characterized by a gradual change in amplitude and twisting of the QRS complexes around the isoelectric line on the electrocardiogram (ECG) [34]. Blocking IKr leads to an increase in the duration of the action potential of ventricular cardiomyocytes, which leads to an excess influx of sodium or a decrease in the outflow of potassium. This excess of positively charged ions leads to an extended phase of repolarization, which leads to a prolongation of the QT interval and is the cause of TdP. This TdP trigger is seen as a premature ventricular complex that is generated during the long repolarization phase (also known as the R-on-T phenomenon). Unlike ventricular fibrillation, TdP is a unique ventricular arrhythmia because it can end spontaneously. However, TdP can transform into ventricular fibrillation and cause SDS [42].

The frequency of AD-induced TdP ranges from 2% to 12% depending on the drug, its dose, duration of administration and the presence of other risk factors [30]. A few studies have shown that data on the frequency of AD-induced TdP in available publications and official public health statistics are underestimated [43]. One reason is that an accurate diagnosis of TdP requires an ECG recording during the heart rhythm disturbance. Another reason is that a significant proportion of patients with TdP do not survive paroxysmal ventricular arrhythmias [43].

Symptoms of AD-induced TdP are like other tachyarrhythmias: palpitations, chest pain, dizziness, dyspnea, hypotension, tachycardia. The ECG pattern is represented by polymorphic ventricular tachycardia against the background of a prolonged QTc interval: long-short trigger sequence on the ECG (ventricular extrasystole (first beat: short) followed by a compensatory pause while the next beat (second beat: long) has a longer QT interval). The diagnosis is made based on ECG data with a characteristic twisting of wide QRS complexes around the isoelectric isoline [14].

It is known that AD-induced TdP can occur at any time of taking this group of drugs in mono- or polytherapy. In the case of intravenous administration of ADs, the development of TdP corresponds to the expected time of peak serum (plasma) concentration of the drug [14]. However, the AD-induced QTc interval prolongation threshold at which TdP is sure to occur is not known. A few studies have demonstrated that a QTc interval of more than 500 msec was associated with a two-fold or three-fold increase in the risk of developing AD-induced TdP, and every 10 msec of QT interval prolongation increases the risk of developing TdP by approximately 5-7% [14]. There is much debate about the susceptibility to fatal cardiac arrhythmias at various levels of QT interval prolongation. Generally, an AD-induced QT prolongation of less than 5 msec is not considered pro-arrhythmic, and a prolongation of 20 msec or more is considered a definite risk factor for TdP [44]. In the case of a homogeneous action of an ADs on the myocardium, the risk of developing TdP is low, despite a significant prolongation of the QTc interval [17] in patients with mental disorders.

It is advisable to assess the initial risk of drug-induced prolongation of the QTc interval, when selecting ADs, their doses and duration of administration. However, in most cases, practitioners prescribe ADs according to the instructions for use in standard doses without considering the individual characteristics of the patient [45, 46], including without pharmacokinetic and pharmacogenetic profiling [47, 48], which can affect the frequency and severity prolongation of the QT interval, risk of TdP and SDS.

Risk of Antidepressant-Induced QT Interval Prolongation

ADs of different pharmacological groups may have a variable risk of the QTc interval prolongation. It depends on pharmacokinetics and pharmacogenetic of ADs and the mechanism of their action on cardiomyocytes (Table 1).

The relationship between AD-induced prolongation of the QTc interval and the development of TdP is ambiguous. To check the risk of developing TdP, you can use the constantly updated list of drugs on the website www.crediblemeds.org or through the CredibleMeds mobile application [49]. CredibleMeds is a non-profit university federal center for education and research in the field of therapy, whose mission is to promote the safe use of drugs [14], including ADs.

All ADs listed in Table 1 were entered into the Crediblemeds.org search engine [49], and then divided into groups according to the risk of developing TdP (Figure 2). However, in addition to a number of unclassified drugs, the CredibleMeds database lacks a number of widely used ADs, both Russian (pipofezin, pirlindol) and foreign-made (agomelatine, amoxapine, tianeptine).

Table 1. Mechanism of action on cardiomyocytes and the effect of antidepressants on the QTc interval in adult patients.

Antidepressant	Mechanism	Effect on QTc Interval	Evidence Class	Authors
A. Monoamine Oxidase Inhibitors				
1. Nonselective Irreversible Monoamine Oxidase Inhibitors				
Isocarboxazid	N/A	N/A	N/A	N/A
Nialamide		N/A	N/A	
Tranylcypromine		N/A	N/A	
Phenelzine		N/A	N/A	
2. Selective Reversible Inhibitors Monoamine Oxidase Type A				
Pirlindole	N/A	N/A	N/A	N/A
Moclobemide	N/A	Prolongation of the QTc interval (toxic dose).	C	[60]
3. Selective Reversible Inhibitors Monoamine Oxidase Type B				
Selegiline	N/A	N/A	N/A	
B. Presynaptic Monoamine Reuptake Inhibitors				
1. Nonselective Presynaptic Monoamine Reuptake Inhibitors				
1.1 Tricyclic Antidepressants				
Amitriptyline	Blockade of the sodium channels. Inhibition of fast current of the potassium slow straightening (IKr). Inhibition of internal slow calcium current. Other mechanisms.	High frequency (23%) of severe prolongation of the QTc interval (≥ 500 msec) at toxic doses.	C	[65, 67, 71]
		Prolongation of the QTc interval (toxic dose)	C	[65, 67, 60]
		Prolongation of the QTc interval. Low risk of SDS.	C	[65, 67, 78]
		Prolongation of the QTc interval.	C	[52, 65, 67, 70, 72]
		Prolongation of the QTc interval.	D	[65, 67, 81-86]
		Prolongation of the QTc interval (by 11.6 msec).	B	[44, 65]
		No significant prolongation of the QTc interval.	B	[74]
		No significant prolongation of the QTc interval. Possible increase in the risk of Brugada`s syndrome.	D	[79]
Imipramine	Blockade of the sodium channels. Inhibition of fast current of the potassium slow straightening (IKr). Inhibition of internal slow calcium current. Other mechanisms.	Often (up to 75%) serious prolongation of the QTc interval (toxic dose).	C	[65, 71]
		Prolongation of the QTc interval.	C	[65, 78]
		Borderline prolongation of the QTc interval (by 11.8 msec).	B	[44, 65]
		Borderline prolongation of the QTc interval.	C	[65, 74]
Clomipramine	Blockade of the sodium channels	Significant prolongation of the QTc interval.	C	[73, 75]
		Borderline prolongation of the QTc interval (by 18.4 msec).	C	[44, 65]
		No significant prolongation of the QTc interval.	C	[65, 74]
		No increase in the risk of SDS.	C	[78]
Pipofezine	N/A	N/A	N/A	N/A
Nortriptyline	Blockade of the sodium channels	Significant prolongation of the QTc interval (by 23.2 msec). High incidence (41%) of severe QTc prolongation (toxic dose).	C	[65, 71]
		Borderline prolongation of the QTc interval (by 10.9 msec).	B	[44, 65]

		Borderline prolongation of the QTc interval.	C	[65, 72, 74]
		No prolongation the QTc interval. Increase in the risk of SDS.	C	[78]
Doxepin		Significant prolongation of the QTc interval (by 30.3 msec). High frequency (33%) of severe prolongation of the QTc interval (toxic dose).	C	[65, 71]
		Borderline prolongation of the QTc interval (by 12.8 msec).	B	[44, 65]
		No significant prolongation of the QTc interval.	C	[74]
Dosulepin		No increase in the risk of SDS.	C	[78]
		No significant prolongation of the QTc interval.	C	[74]
Desipramine		Borderline prolongation of the QTc interval (by 11.4 msec).	B	[44]
Trimipramine		Borderline prolongation of the QTc interval (by 18.6 msec).	C	[44]
Protriptyline		N/A	N/A	N/A
1.2. Selective Norepinephrine Reuptake Inhibitors or Tetracyclic Antidepressants*				
Maprotiline	Blockade of the sodium channels.	Borderline prolongation of the QTc interval.	B	[65, 74, 87, 88]
2. Selective Monoamine Reuptake Inhibitors				
2.1. Selective Serotonin Reuptake Inhibitors				
Paroxetine	Blockade of the sodium channels. Blockade of hERG potassium channels.	Borderline prolongation of the QTc interval (by 12.4 msec).	B	[44, 65]
		Significant prolongation of the QTc interval.	C	[65, 92, 101]
		No significant prolongation the QTc interval. No increase in the risk of SDS.	B	[78]
		No significant prolongation of the QTc interval.	C	[96 - 98, 101]
Sertraline	No blockade of the sodium channels. Blockade of hERG potassium channels.	Borderline prolongation of the QTc interval (more than 10 msec) at toxic doses.	A	[102]
		Borderline prolongation of the QTc interval (by 11.6 msec).	B	[44]
		Significant prolongation of the QTc interval. Increase in the risk of TdP.	C	[99]
		Significant prolongation of the QTc interval. Increase in the risk of TdP.	C	[77]
		Significant prolongation of the QTc interval. No increase in the risk of SDS.	C	[78]
		No significant prolongation of the QTc interval.	C	[96 – 98, 101]
Fluvoxamine	Blockade of the sodium channels Blockade of hERG potassium channels.	Shortening of the QTc interval.	C	[65, 78]
		No significant prolongation of the QTc interval.	C	[96 - 98, 101]
Fluoxetine	Blockade of hERG potassium channels.	Borderline prolongation of the QTc interval (by 13.0 msec).	B	[44]
		Borderline prolongation of the QTc interval (by 12.2 msec) at toxic doses.	C	[71]
		No prolongation of the QTc interval. No increase in the risk of SDS.	C	[78]
		No significant prolongation of the QTc interval.	C	[96 – 98, 101]
Citalopram	No blockade of the	Significant prolongation of the QTc interval.	A	[65, 106]

	sodium channels. Blockade of hERG potassium channels.	Borderline prolongation of the QTc interval (by 10.4 msec).	B	[44, 65]
		Significant prolongation of the QTc interval.	C	[65, 70, 78, 96, 98]
		Significant prolongation of the QTc interval (by 21.7 msec). Severe prolongation of the QTc interval frequently (25%) at toxic doses.	C	[65, 71]
		Significant prolongation of the QTc interval (toxic dose)	C	[65, 74]
		No significant prolongation of the QTc interval.	C	[94, 97]
Escitalopram	No blockade of the sodium channels. Blockade of hERG potassium channels.	Significant prolongation of the QTc interval.	C	[65, 70, 78, 98, 101]
		Severe prolongation of the QTc interval frequently (23%) at toxic doses.	C	[71]
		No significant prolongation the QTc interval. Increase in the risk of SDS.	C	[80]
		No causes significant prolongation of the QTc interval.	C	[96, 97]
2.2. Selective Norepinephrine Reuptake Inhibitors				
Atomoxetine	Blockade of hERG potassium channels.	Significant prolongation of the QTc interval in female.	C	[108]
		Significant prolongation of the QTc interval.	C	[111]
Viloxazine		No significant prolongation the QTc interval.	A	[112]
Reboxetine	N/A	N/A	N/A	N/A
Teniloxazine	N/A	N/A	N/A	N/A
2.3. Selective Dopamine and Norepinephrine Reuptake Inhibitors				
Bupropion	Blockade of hERG potassium channels.	Prolongation of the QTc interval. Low frequency (19%) of prolongation of the QTc interval (toxic dose).	C	[71]
		Prolongation of the QTc interval (toxic dose).	C	[113]
		No significant prolongation of the QTc interval.	C	[78]
		Shortening of the QTc interval.	C	[70]
2.4. Selective Serotonin and Norepinephrine Reuptake Inhibitors				
Venlafaxine	No blockade of the sodium channels. Other mechanisms.	Borderline prolongation of the QTc interval (by 10.6 msec).	B	[44, 65]
		Significant prolongation of the QTc interval.	C	[52, 65, 113]
		Increase in the risk of TdP.	C	[65, 77]
		No significant prolongation of the QTc interval (by 3.8 msec). Low frequency (13%) of prolongation of the QTc interval (toxic dose).	C	[65, 71]
		Significant prolongation of the QTc interval. Increase in the risk of SDS (polytherapy).	C	[65, 78]
		Doesn't cause significant prolongation of the QTc interval.	C	[97, 118]
Desvenlafaxine	N/A	Significant prolongation of the QTc interval.	C	[118]
		No significant prolongation of the QTc interval (monotherapy). Possible prolongation the QTc interval (polytherapy).	C	[78]
Duloxetine	Blockade of the sodium channels.	No significant prolongation the QTc interval.	C	[33, 78, 118]
		Significant prolongation of the QTc interval.	C	[117]
Milnacipran	N/A	No significant prolongation of the QTc interval.	C	[118]

Levomilnacipran		No significant prolongation of the QTc interval.	B	[115]
		Significant prolongation of the QTc interval.	C	[116]
Ansofaxin		N/A	N/A	N/A
Nefopam				
C. Antidepressants with Predominant Effects on Receptor Systems				
1. Serotonin and alpha-2 adrenoceptor antagonists				
1.1 Antagonists of alpha-2-adrenergic receptors and 5-HT2a- and 5-HT3-receptors				
Mianserin	No blockade of the sodium channels. Blockade of hERG potassium channels.	Significant prolongation of the QTc interval.	C	[59, 65, 73]
1.2. Antagonists of 5-HT2a and 5HT-2c Receptors and Alpha-2-Adrenergic Receptors				
Mirtazapine	No blockade of the sodium channels. Other mechanisms.	Significant prolongation of the QTc interval. Increase in the risk of SDS.	C	[59, 65, 122]
		Significant prolongation of the QTc interval.	C	[59, 125]
		Increase in the risk of TdP. Increase in the risk of SDS.	C	[59, 113, 129]
		Significant prolongation of the QTc interval (toxic dose).	A	[59, 123]
		Significant prolongation of the QTc interval (toxic dose).	C	[59, 80]
		No significant prolongation of the QTc interval.	A	[59, 118]
		No significant prolongation of the QTc interval.	C	[59, 78]
1.3. 5-HT1a Receptor Agonist, 5-HT2a- and 5-HT2c-Receptor Antagonist and Alpha-1-Adrenergic Blocker				
Trazodone	Blockade of all major ion channels (IKr, IKs, INa and ICa), especially the potassium channel hERG.	Significant prolongation of the QTc interval.	C	[124, 129, 132, 134, 135, 180]
		Significant prolongation of the QTc interval. Increase in the risk of TdP.	C	[132, 133, 180]
		Borderline prolongation of the QTc interval (by 12.0 msec). High frequency (24%) of the QTc interval prolongation (toxic doses).	C	[71, 132, 180]
		Significant prolongation of the QTc interval (toxic doses).	C	[80, 132, 180]
		No significant prolongation the QTc interval.	C	[78, 126, 132, 180]
1.4. 5-HT1a Receptor Partial Agonist with Serotonin Reuptake Inhibition				
Vilazodon	N/A	No significant prolongation the QTc interval.	C	[59, 136]
1.5. 5-HT2a and 5-HT2c receptor antagonist and Serotonin Reuptake Inhibitor				
Nefazodon	Blockade of the potassium channel hERG and other ion channels (IKr, IKs, INa and ICa).	Significant prolongation of the QTc interval.	C	[135, 181]
1.6. 5-HT1 Receptor Agonists				
Gepiron	N/A	N/A	N/A	
Tandospirone				
2. Melatonin MT1 and MT2 receptor agonist and Serotonin 5-HT2b and 5-HT2c receptor antagonist				
Agomelatine	No blockade of the	No significant prolongation the QTc interval.	A	[59, 65, 127]

	sodium channels.	No Significant prolongation the QTc interval.	C	[59, 65, 118, 128]
D. Antidepressants Mixed (Multimodal), Other or Not Enough Learned Mechanism of Action				
1. Serotonin Reuptake Inhibitor and 5-HT1a Receptor Agonist, 5-HT1B Receptor Partial Agonist, 5-HT3 Receptor Antagonist, 5-HT7 Receptor Antagonist				
Vortioxetine	N/A	No significant prolongation of the QTc interval.	A	[59, 140, 181]
		Not significant prolongation the QTc interval.	C	[59, 138, 139, 141, 181]
2. S-Adenosylmethionine Derivative				
Ademetionine	N/A	N/A	N/A	N/A
3. Facilitation of Serotonin Reuptake with Blockade of Its Destruction				
Tianeptine	N/A	N/A	N/A	N/A
4. Serotonin and Norepinephrine Reuptake Inhibitor and Serotonin Receptor Antagonist with Potent Antipsychotic Blockade of D2 Receptors				
Amoxapine	N/A	N/A	N/A	[59]

Note: QTc – corrected QT; N/A – not available; TdP - Torsades de Pointes; SDS - sudden death syndrome; D2 - dopamine receptor subtype 2; 5-HT1 - 5-hydroxytryptamine receptor subtype 1; 5-HT1a - 5-hydroxytryptamine receptor subtype 1a; 5-HT1b - 5-hydroxytryptamine receptor subtype 1b; 5-HT3 - 5-hydroxytryptamine receptor subtype 3; 5-HT7 - 5-hydroxytryptamine receptor subtype 7; MT1 - melatonin *receptor* subtype 1; MT2 - melatonin *receptor* subtype 2; IKr - rapidly activating delayed rectifier potassium channels; IKs - slowly activating delayed rectifier potassium channels; INa - sodium current; ICa - *calcium* current; hERG - the human ether-a-go-go-related gene.

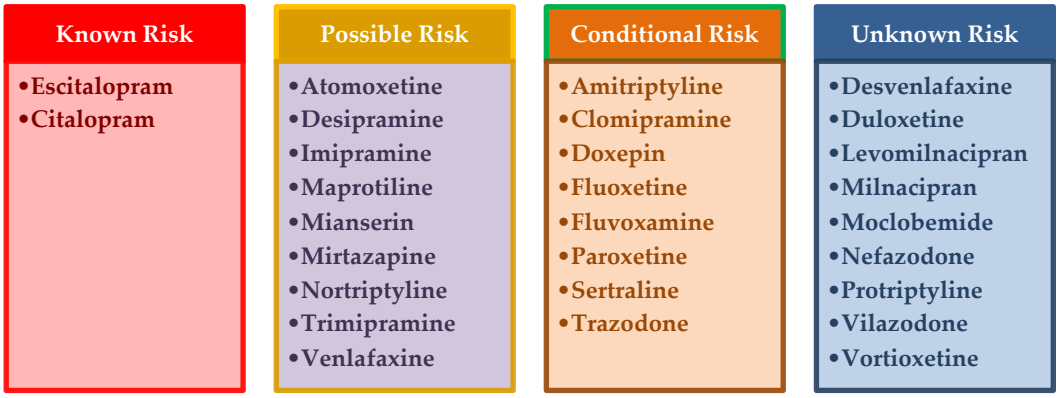

Figure 2. Risk of developing antidepressant-induced Torsades de Pointes.

Note: red box - known risk: there is strong evidence to support the conclusion that these ADs prolong the QTc interval and are clearly associated with a risk of TdP, even when taken according to official instructions; orange block - possible risk: there is strong evidence to support the conclusion that these ADs may cause QTc prolongation, but there is currently insufficient evidence that these ADs, when used according to official package directions, are associated with a risk of developing TdP; green box - conditional risk: there is substantial evidence that supports the conclusion that these ADs are associated with a risk of TdP, but only under certain conditions (eg, overdose, hypokalemia, congenital long QTc interval, or drug-drug interactions that result in prolongation of the QTc interval); blue block - not classified: these ADs are not reviewed by CredibleMeds, but currently available evidence has not led to a decision to classify them in any of the ventricular tachycardia risk categories; this does not indicate that this ADs is not associated with a risk of QTc prolongation or TdP, as it may not have been adequately tested for these risks in patients (prepared by the authors using available data from CredibleMeds, last revised date of the QTdrugs list: February 21, 2023 [49]).

The incidence of AD-induced QTc prolongation depends on the pharmacological group and the specific drug, as well as on other modifiable and non-modifiable risk factors [14, 17, 24, 30, 50-52] (Table 2).

Table 2. Risk factors for antidepressant-induced QTc prolongation and development of Torsades de Pointes.

Modifiable Risk Factors	Non-Modifiable Risk Factors
Electrolyte disorders (hypokalemia, hypomagnesemia, hypocalcemia).	Age over 65 years.
Treatment with diuretics.	Female.
Rapid intravenous administration of ADs. that prolongs the QT interval.	Congenital long QT syndrome (causal mutations). Familial forms of long QT syndrome (causal mutations).
	Multifactorial long QT syndrome.
Inadequate dosing of ADs that prolongs the QT interval in acute kidney injury or chronic kidney disease.	Genetic predisposition to AD-induced QT prolongation (genetic polymorphisms of the candidate genes encoding voltage-dependent ion channels).
Use of ADs that prolong the QT interval.	Genetic predisposition to slow down the metabolism of the ADs and/or slow down its efflux (genetic polymorphisms of the candidate genes encoding key metabolic enzymes and transport proteins of ADs).
Drug-drug interactions.	Increase in the QTc interval > 60 msec compared with the value before ADs treatment.
	QTc interval > 500 msec after ADs treatment.
	Bradycardia before or after ADs treatment.
	Heart disease (myocardial infarction, chronic heart failure, left ventricular failure, heart failure with reduced ejection fraction). Recent cardioversion.
	Thyroid diseases (decompensated).
	Impaired kidney function (chronic renal failure).
	Elevated serum CRP.

Note: ADs – antidepressants; CRP – C-reactive protein; QTc – corrected QT.

Risk factors are important in predicting the development of AD-induced prolongation of the QTc interval and TdP. Compared with patients without risk factors, the odds ratio (OR) of QTc interval prolongation in patients with one risk factor is 3.2 (95% confidence interval [CI] 2.1–5.5). The OR increases markedly in patients with two or three or more risk factors (7.3 [4.6–11.7] and 9.2 [4.9–17.4], respectively [30]. According to the of "reduced repolarization reserve" proposed by Roden [53], a combination of risk factors is needed to overcome the complex and compensatory physiological mechanisms (reserve or redundancy) that interact to maintain normal ventricular concept repolarization.

The Tisdale`s Scale [54] (Figure 3) can be used to assess the risk of AD-induced QTc prolongation and the risk of developing TdP. However, it has been validated for intensive care patients.

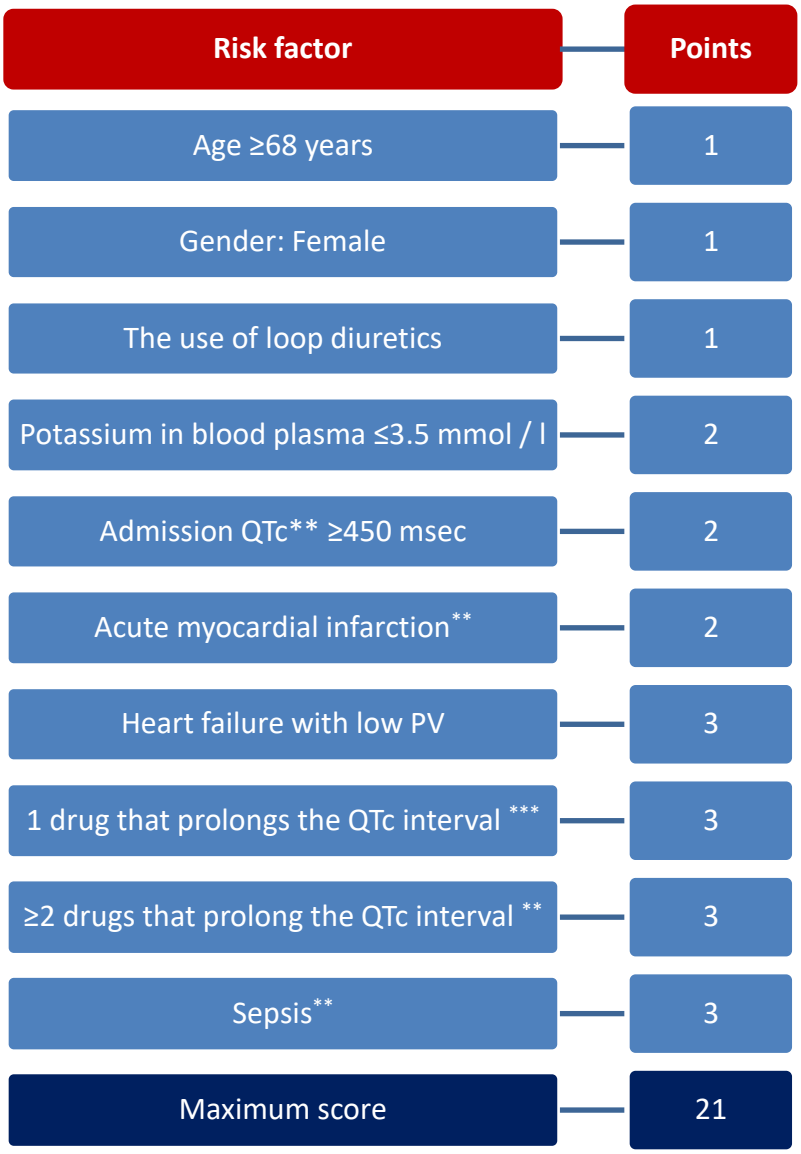

Figure 3. Tisdale`s scale. Note: ** During an acute event/illness; The QTc interval usually returns to normal after resolution; *** 3 points for taking 1 AD that prolongs the QTc interval; 3 additional points for taking ADs that prolong the QT interval ≥2 sec (6 points in total). Risk assessment category (number of points): low risk < 7 points; moderate risk 7–10 points; high risk > 11 points.

Monoamine Oxidase Inhibitors

Drugs of this class were the first to be used as ADs, marking the beginning of this group of psychotropic drugs [55]. Monoamine oxidase inhibitors (MAOIs) are divided into non-selective and selective, reversible or irreversible. The first generation of irreversible and non-selective MAOIs resulted in serious ADRs such as hepatotoxicity and tyrosine syndrome. This has led to the development of selective and reversible MAO-A and MAO-B inhibitors with an improved safety profile [56]. The class of non-selective MAO inhibitors includes nialamide, phenelzine, tranylcypromine, isocarboxazid. Selective reversible MAO inhibitors type A include pirlindol and moclobemide; MAO type B - selegiline [56-59].

During the analyzed period of time, we found only one publication on the effect of this group of ADs on the QTc interval, the risk of developing TdP and SDS. According to

a study by Yekehtaz et al. overdose of moclobemide can lead to prolongation of the QTc interval, predisposing to ventricular tachyarrhythmia and TdP [60]. Also, moclobemide is included in the list of CredibleMeds [49], but belongs to the group of "unclassified" drugs.

Presynaptic Monoamine Reuptake Inhibitors

Further search for ADs with other mechanisms of action and, accordingly, a safer profile led to the development of the most extensive group - presynaptic monoamine reuptake inhibitors. This group includes two large subgroups of non-selective and selective inhibitors of presynaptic monoamine uptake.

Tricyclic Antidepressants

The class of tricyclic antidepressants (TCAs) includes amitriptyline, clomipramine, imipramine, nortriptyline, doxepin, dosulepine, desipramine, trimipramine, pipofezin, and protriptyline [62, 63].

TCAs are known to prolong the QTc interval mainly by blocking sodium channels. This effect is more pronounced with the combined use of TCAs with potassium channel blockers [64-66]. In addition to blockade of sodium channels [65], amitriptyline and imipramine inhibit fast potassium current of delayed rectification (IKr) [67] and internal slow calcium current [68], which leads to delayed cardiomyocyte membrane repolarization and possible prolongation of the QTc interval. The effect of TCAs and tetracyclic antidepressants on the QTc interval may also be due to their anticholinergic effects [61]. TCAs slow down the rate of conduction of electrical excitation through the bundles of His and its branches, which increases the QRS complex and the duration of the QT interval [69].

We found 17 studies on the effect of TCAs on QTc, conducted in the USA [44, 70, 71], Japan [72, 73], the Netherlands [74], Denmark [65], Germany [52], and Spain [75]. Sample sizes ranged from 8769 to 5953141 people. The age of the observed patients ranged from infancy [44] to 78 years [52]. All studies included male and female patients. The duration of ADs use varied from 62 days [72] to several years [70]. QTc was calculated using both the Bazett formula [52, 71] and the Frederic formula [73, 74]. In a study by Iribarren C et al. used log-linear regression of raw QT per RR interval instead of standard QTc duration formulas, and then fitted adjustment equations within 98 strata to obtain sex- and age-specific QT values adjusted for HR by sex and race/ethnicity of patients [44]. The ethnic diversity of patients was also documented in a study by Campleman et al. [71], which may affect the outcome of the study.

However, the largest number of studies (15 out of 17) of TCAs was devoted to amitriptyline. It has been suggested that amitriptyline's potent inhibition of Nav1.5 sodium channels in cardiomyocytes is an important mechanism for its cardiotoxicity [76]. According to the results of most studies, amitriptyline caused a significant prolongation of the QTc interval [52, 70, 72]. Only the study by Noordam et al. found no prolongation of the QTc interval when taking this AD [74]. The authors of this study hypothesized that an increase in HR due to the anticholinergic properties of TCAs leads to an incorrect calculation of the duration of the QTc interval using the Bazett formula and an overestimation of the prolongation of the QTc interval when taking TCAs. To do this, QT interval duration in 12734 participants in the prospective population-based Rotterdam study was adjusted for heart rate according to Bazett (QTcBazett), Fridericia (QTcFridericia), or regression coefficient (QTcStatistical). Based on the results of the study, the authors conclude that there is probably no relationship between taking TCAs and prolongation of the QTc interval and the preference for calculating QTc using the Frideric formula [74]. However, in a study by Okayasu et al., the calculation of the duration of the QTc interval was also carried out using the Fridericia formula. But the authors, on the contrary, concluded that there was a dose-dependent prolongation of the QTc interval when taking amitriptyline [73]. Such a difference in the results of previous studies may be

due to both the different design of studies and the difference in the age and ethnic composition of the samples.

When taking therapeutic doses of amitriptyline, prolongation of the QTc interval can reach a borderline level (from 10 to 20 msec) [44], rarely clinically significant [72], and therefore amitriptyline has a low risk of developing TdP [77] and other cardiac conduction disorders, as well as SDS [78]. However, in an experiment by Lubna et al. when dogs were given a toxic dose of amitriptyline, the risk of developing Brugada syndrome was higher than the risk of QTc prolongation [79]. There is no doubt a significant prolongation of the QTc interval when taking amitriptyline in toxic doses [71, 80]. This fact is used in laboratory studies in rats to model QTc interval prolongation and cardiotoxicity with the administration of high doses of amitriptyline [81-86].

Among the five studies on clomipramine, one study using the Fridericia QTc interval calculation found no significant prolongation of the QTc interval [74]. Other studies have found clomipramine-induced prolongation of the QTc interval [44, 75] with a very rare development of TdP [77]. A study by Okayasu et al. revealed an increased risk of SDS with clomipramine [73]. At the same time, Aronow et al. deny the risk [78].

According to the results of four studies, imipramine caused a significant prolongation of the QTc interval in both men and women of all age groups [44, 78], including when recalculating the QTc interval according to Frederick's formula [74], and especially at toxic doses [71].

In 4 out of 5 studies, nortriptyline caused QTc prolongation [44, 71-73]. Only in the study by Aronow et al. no statistically significant prolongation of the QTc interval was found, but an increase in the risk of SDS was found when taking nortriptyline [78].

Three studies of the effect of doxepin on the QTc interval showed conflicting results, ranging from no QTc interval prolongation [74] to prolongation of the QTc interval to borderline values [44] at therapeutic doses and a significant frequent QTc interval prolongation with the appointment of this AD at toxic doses [71]. The development of TdP in patients was very rare [77].

The results of two studies of dosulepine demonstrated that this AD does not cause a significant prolongation of the QTc interval [74] and does not increase the risk of SDS [78]. According to a study by Iribarren et al., desipramine and trimipramine caused prolongation of the QTc interval to the borderline level [44]. We did not find any studies of the effect of pipofezin and protriptyline on the QTc interval during the analyzed period.

Tetracyclic Antidepressants

In a number of countries, maprotilin belongs to the group of tetracyclic (heterocyclic) ADs [87]. In other countries, this AD is classified as a selective norepinephrine reuptake inhibitor [88]. According to a study by Noordam et al., maprotiline causes borderline prolongation of the QTc interval [74]. This effect may be due to blockade of sodium channels in cardiomyocytes [65].

Selective Monoamine Reuptake Inhibitors

This subgroup of presynaptic monoamine reuptake inhibitors includes selective serotonin reuptake inhibitors (SSRIs), norepinephrine, dopamine and selective serotonin and norepinephrine reuptake inhibitors (SNRIs). The results of previous studies in this subgroup as a whole and for individual ADs in this subgroup vary widely from no effect on the QTc interval to a high frequency of its significant lengthening, especially at a toxic dose, up to an increased risk of TdP and SDS.

Selective Serotonin Reuptake Inhibitors

SSRIs include paroxetine, sertraline, fluvoxamine, fluoxetine, citalopram, and escitalopram [62, 63]. All these ADs are widely used in clinical practice for the treatment of depressive, anxiety disorders, and eating disorders [89] in the world [90]. It is believed that SSRIs prolong the QTc interval through two mechanisms: direct blockade of hERG

potassium channels and impaired expression of the hERG protein on the cell membrane of cardiomyocytes. The second effect reduces the flux of potassium ions by reducing the number of hERG ion channels [64, 68, 91]. Sertraline, citalopram, and escitalopram do not block sodium channels, unlike fluvoxamine, fluoxetine, and paroxetine, which block them [65]. Paroxetine significantly reduces the rapid current of sodium ions through the membrane of human left ventricular cardiomyocytes due to the inhibition of Nav1.5 channels, which leads to a slowdown in conduction and a decrease in the excitability of cardiomyocytes [92].

We found 15 studies on the effect of SSRIs on the QT interval, conducted in the USA [44, 70, 71, 80, 93, 94], Japan [73, 95], the Netherlands [96, 97], Denmark [65], France [98], Sweden [43], Germany [77]. Sample sizes varied from 1 clinical case [95, 99] to 618450 [93] patients with mental disorders. The age of the observed patients ranged from infancy [44] to 89 years [100]. All studies included male and female patients. The duration of ADs use varied from 17 days [95] to several years [70, 93, 96]. QTc was calculated using Bazett's formula [71], Frederick's formula [73, 96], and log-linear regression of raw QT on RR in a study by Iribarren et al. [44].

Among 7 studies of paroxetine, two publications, one of which was a clinical case of a 43-year-old woman from Japan who took paroxetine at the maximum therapeutic dose of 50 mg for 17 days [95], described prolongation of the QTc interval [44]. However, in most studies, paroxetine did not cause QTc prolongation [78, 96-98, 101] and SDS [78].

Mixed results have been obtained in studies of sertraline. In 4 of 9 studies, sertraline-induced prolongation of the QTc interval was not found [96–98, 101]. However, 5 studies have demonstrated QTc prolongation from borderline values with therapeutic doses [44, 78], which occur rarely [77], to a significant prolongation of the QTc interval with sertraline at toxic doses [102]. The latest study was conducted by the manufacturer and is grade A evidence [102]. At the same time, some authors did not find an increase in the risk of sertraline-induced SDS [78], other authors found rare cases of TdP [77] when taking sertraline. As described by Ott et al. reported a clinical case in a 40-year-old Indian woman who was taking sertraline at a dose of 50 mg/day and developed ventricular fibrillation with cardiac arrest against the background of a significantly prolonged QTc interval [99]. However, it is not possible to assess the role of sertraline in the fatal outcome, since there were no examination results, including ECG, before the start of therapy, and at the time of loss of consciousness, which served as a reason for hospitalization, the patient had leukocytosis, severe anemia, hyperglycemia, hyponatremia, hypocalcemia, renal failure, increased liver transaminases and metabolic acidosis, which indicates a deep decompensation of a somatic state of unknown origin.

Four studies have demonstrated that fluvoxamine does not prolong the QTc interval [96–98, 101]. In a study by Aronow et al. showed shortening of the QTc interval [78].

In 5 of 7 studies with fluoxetine, QTc interval prolongation was not found [78, 96–98, 101]. However, two studies documented borderline prolongation of the QTc interval with fluoxetine at therapeutic doses [44] and toxic doses [71].

In 2011, following post-marketing surveillance, the FDA issued several warning statements about the risk of QT prolongation and TdP with citalopram, stating that citalopram should not be given in doses greater than 40 mg/day [103, 104]. The European Medicines Agency issued a similar safety warning in 2011 [105]. Eight studies conducted during the analyzed period confirmed the prolongation of the QTc interval when taking citalopram in both toxic [71, 80] and therapeutic doses [44, 78, 96, 98, 106], with a dose-dependent effect [69, 70, 73]. However, the authors of two studies did not find QTc prolongation in people over 60 years of age when taking citalopram [94, 97].

Escitalopram is the S-enantiomer of citalopram. 5 of 8 studies of escitalopram have shown prolongation of the QTc interval [71, 78, 98, 101] with a dose-dependent effect [70, 73]. However, no QTc prolongation was found in three studies [80, 96, 97]. The results of studies of the risk of SDS with citalopram and escitalopram compared with other SSRIs are directly opposite: from the absence, including among patients aged 60 years and with

cardiovascular risk factors [73, 107], to an increased risk of SDS within 1 year of use these ADs [80, 91]. Eroglu et al. in a study of sudden death in 2258 Danes taking citalopram and escitalopram, found an association of SDS with reported blood pressure in men but not in women [65]. The frequency of CDS increased when taking high doses of citalopram (>20 mg) and high doses of escitalopram (>10 mg; OR 1.46 [95% CI 1.27–1.69], OR 1.43. [95% CI 1.16–1.75], respectively [65].

Paradoxical results were obtained by Zivin et al. [93] in a large cohort study of cardiac events in US men treated with citalopram and sertraline. The risk of ventricular arrhythmia and SDS was lower with citalopram greater than 40 mg/day than with less than 20 mg/day and sertraline greater than 100 mg/day [93]. This may be due to the fact that the design of the studies did not take into account the presence of cardiovascular disease in patients at the time of prescription of these ADs. Low doses of these drugs may have been prescribed by the doctor due to comorbidity, which led to more frequent cardiac accidents later on.

Danielson et al. analyzed 410 reported cases of TdP in Sweden from 2006 to 2017 [43]. The authors found that TdP was much more common in people ≥ 65 years of age, on ADs than on other drugs, and in younger patients. Among ADs, a significantly higher incidence of TdP was found with citalopram [43]. Overall, CredibleMeds [49] classifies citalopram and escitalopram as ADs with a "known risk" of QTc prolongation and TdP.

Selective Norepinephrine Reuptake Inhibitors

The SNRI class includes atomoxetine [62, 63] and new ADs viloxazine, reboxetine, and teniloxazine.

Of interest is the study by Suzuki et al. [108], in which among 41 Japanese patients treated with atomoxetine for at least 2 weeks, prolongation of the QTc interval was observed only in women. A significant positive correlation was observed between the dose of atomoxetine and QTcB in women, as well as a slightly significant positive correlation between the dose of atomoxetine and QTcF. However, no correlation between plasma concentrations of atomoxetine and QTc interval was found in either women or men [108]. The authors explain the results obtained by the influence of sex hormones on the length of the QTc interval. It is shown that the QTc interval decreases with an increase in the level of endogenous testosteron. Thus, men can be protected from the prolongation of the QTc interval caused by atomoxetine, due to the relatively high levels of dough-sterone in plasma [109]. Scherer et al. we drew attention to some limitations of this study: a small sample size, the absence of pharmacogenetic testing of mutations in the gene encoding hERG, the blockade of which may explain the lengthening of the QTc interval when taking atomoxetine [110]. The difference in the distribution of causal mutations of this gene between male and female patients could affect the risk of negative effects of atomoxetine on the QTc interval. However, QTc prolongation with atomoxetine is rare [111].

Viloxazine does not cause QTc prolongation in a Class A study [112]. Publications on the effect on the QTc interval of reboxetine and teniloxazine were not found for the specified period.

Selective Dopamine and Norepinephrine Reuptake Inhibitors

This class of ADs includes bupropion [62, 63]. According to some studies, bupropion at toxic doses causes prolongation of the QTc interval [71, 113]. The prolongation of the QTc interval in case of an overdose of bupropion is due to its I(Kr)-blocking effect. At the same time, bupropion practically does not affect I(Ks) and I(Na). It has been shown that the QRS expansion when taking bupropion is not associated with the blockage of cardiac sodium channels [114]. Therapeutic doses of bupropion do not prolong the QTc interval [78] and even shorten it [70].

Selective Serotonin and Norepinephrine Reuptake Inhibitors

SNRIs include milnacipran, levomilnacipran, duloxetine, venlafaxine, desvenlafaxine, ansofaxine, and nefopam [62, 63]. We found 11 studies on the effect of SNRIs on the QTc interval conducted in the USA [44, 71, 113, 115], China [116], Australia [117], Germany [52, 77], the Netherlands [97]. Sample sizes ranged from 1 patient [117] to 59467 patients [44]. The age of the observed patients ranged from infancy [44] to 80 [115]. All studies included male and female patients. During the indicated period, one study of the cardiotoxic effects of milnacipran was found, in which prolongation of the QTc interval was not detected when taking it [118].

Prolongation of the QTc interval in patients taking ADs of this subgroup is associated with blockade of sodium channels of cardiomyocytes [119].

Two studies of the enantiomer of milnacipran (levomylnacipran [120]), one of which was a phase III clinical trial [115], showed no or negligible prolongation of the QTc interval [116]. In two of three studies, duloxetine did not prolong the QTc interval [78, 118]. Isbister et al. described two clinical cases of abnormal QT interval when taking duloxetine at a dose above 120 mg/day [117]: lengthening with bradycardia and shortening with tachycardia. However, it is not clear from the content of the article whether the correction of the duration of the QT interval relative to the HR was carried out.

Among the SNRIs, venlafaxine has attracted the greatest interest from researchers. Eight studies focused on the effect of venlafaxine on the QTc interval. Two of them did not show prolongation of the QTc interval [97, 118]. However, therapeutic doses of venlafaxine have been associated with borderline prolongation of the QTc interval [44] and a rare, slight prolongation of the QTc interval with toxic doses of this AD [71]. In four studies, venlafaxine caused significant QTc prolongation [52, 113] with rare cases of TdP [77] and SDS in polytherapy [78]. The risk of QTc prolongation is increased in elderly patients with cardiovascular disease taking concomitant therapy [69]. An association between venlafaxine serum concentration and QTc interval duration has not been found [86]. The active metabolite of venlafaxine [121], desvenlafaxine, caused a significant prolongation of the QTc interval [118]. Another study clarifies that desvenlafaxine does not prolong the QTc interval when used alone, but may prolong the QTc interval when polytherapy [78].

No studies of ansofaxin and nefopam were found during the specified period.

Antidepressants with Predominant Effects on Receptor Systems

This group of ADs includes agonists of serotonin and melatonin receptors, antagonists of serotonin and adrenergic receptors [62, 63]. We found 23 studies on the effect of this group of blood pressure on the QTc interval, conducted in the USA [71, 80, 113, 122–124], Japan [73, 125], Canada [126], Denmark [65], France [127], Sweden [43], Great Britain [128], Switzerland [129]. Sample sizes varied from 1 clinical case [124, 125] to 1630 patients [126]. The age of the observed patients ranged from 18 [127] to 83 years [125]. All studies included male and female patients.

Serotonin and Alpha-2 Adrenoreceptor Antagonists

This class of ADs includes mianserin and mirtazapine [62, 63]. It is believed that mianserin and mirtazapine do not block sodium channels [65]. During this period, only one study by Okayasu et al was found, according to which mianserin caused a significant prolongation of the QTc interval [73]. Scherer et al. were found that mianserin inhibits potassium currents of hERG in a dose-dependent manner in the open and inactivated state. At the same time, the inhibitory effect was not reversible after elimination of the drug [130]. In two out of nine studies, mirtazapine did not prolong the QTc interval [78, 118] or slightly prolonged it by less than 5 msec at high doses of 45 mg/day and 75 mg/day [123]. Three studies documented significant prolongation of the QTc interval with mirtazapine at therapeutic doses [122], including a low dose (15 mg/day) in an 83-year-old male from Japan [125] and toxic doses [80]. The authors of four studies concluded that mirtazapine-induced increased risk of TdP and SDS [65, 113, 122, 131]. Eroglu et al. found

an increase in the frequency of CDS when taking high doses of mirtazepine (>30 mg; OR 1.59 [95% CI 1.18-2.14]) [65].

Serotonin Receptor Antagonists and Agonists

This class of ADs includes trazodone, vilazodone, and nefazodone [62, 63]. The largest number of studies are devoted to trazodone. This AD is often used off-label to induce sleep in people with depression, anxiety, substance abuse, and bulimia [124]. Recently, there has been interest in the use of trazodone for the treatment of Alzheimer's disease and associated non-cognitive symptoms of dementia [126]. *In vitro* data show strong inhibitory activity of trazodone on all major ion channels (IKr, IKs, INa and ICa) with particularly high inhibitory activity on the hERG potassium channel [68, 132].

Two of nine trazodone publications reported no significant QTc prolongation [78, 126]. However, Armstrong et al. found that male gender was a statistically significant risk factor for QTc prolongation with trazodone among elderly patients [126]. Four studies have shown QTc prolongation with trazodone at therapeutic doses [124, 129, 133, 134] and three studies at toxic doses [71, 80, 135]. A moderate dose-dependent effect was found, in which there was no prolongation of the QTc interval when using trazodone at a dose of 20 mg/day, but there was a significant prolongation at doses of 60 mg/day and 140 mg/day [129]. Soe et al. concluded on one clinical case that the risk of developing TdP was increased when taking trazodone [133].

One study of vilazodone and nefazodone found that vilazodone [136] does not cause QTc prolongation, while nefazodone causes QTc prolongation [137]. Nefazodone has been shown to inhibit various voltage-gated ion channel currents, including IKr, IKs, INa, and ICa, but the main mechanism for QT interval prolongation is the hERG potassium channel blockade [137].

5HT1 Serotonin Receptor Agonists

Information on the effect of hespirone and tandospirone on the QTc interval was not found.

Melatonin Receptor Agonists

This class includes an AD unique in its mechanism of action - agomelatine. *In vitro* receptor binding studies have shown that agomelatine has a very low affinity for any of the tested ion channels, including no effect on the hERG potassium channel [127] and sodium channels [65]. Studies on agomelatine are few, probably due to the fact that, unlike Russia, Europe and Australia. This AD is not approved for use in the US and Canada due to the low level of evidence [59]. Three studies show that agomelatine does not prolong the QTc interval [118, 127, 128].

Antidepressants with a Mixed (Multimodal), Other or Poorly Understood Mechanism of Action

This group of ADs includes vortioxetine and ademetionine, tianeptine and amoxapine. In four studies on vortioxetine, no prolongation of the QTc interval was found [138-141]. Information on the effect of ademetionine, tianeptine and amoxapine on the QTc interval was not found.

The role of Pharmacogenetics and Pharmacokinetics of Antidepressants in the QTc Interval Prolongation

The pharmacokinetics of ADs and the associated levels of drugs in the blood may explain the dose-dependent risk of AD-induced prolongation of the QTc interval, especially for TCAs [73].

Table 4. Characteristics of antidepressant doses and their reference level in the blood

Antidepressant	Initial dose (mg/day)	Average therapeutic dose (mg/day)	Maximum dose (mg/day)	Therapeutic blood level (ng/ml)	References
A. Monoamine Oxidase Inhibitors					
1. Nonselective Irreversible Monoamine Oxidase Inhibitors					
Isocarboxazid	20	40	60		[182]
Nialamide	N/A	N/A	N/A		N/A
Tranylcypromine	N/A	30	60		[182]
Phenelzine	N/A	N/A	N/A		N/A
2. Selective Reversible Inhibitors Monoamine Oxidase Type A					
Pirlindole	50 - 75	150 - 300	400		[57]
Moclobemide	300	300 - 600	600		[57]
3. Selective Reversible Inhibitors Monoamine Oxidase Type B					
Selegiline	6	6	12		[182]
B. Presynaptic Monoamine Reuptake Inhibitors					
1. Nonselective Presynaptic Monoamine Reuptake Inhibitors					
1.1 Tricyclic Antidepressants					
Amitriptyline	25 - 50	150 - 200	300	50 - 250	[182]
Imipramine	75	150 - 200	300	33 - 85	[182]
Clomipramine	50 - 75	100 - 150	250	20 - 175	[182]
Pipofezine	25 - 50	150 - 200	500	24.5	[57]
Nortriptyline	25 - 50	75 - 100	150	50 - 150	[182]
Doxepin	3	6	6	N/A	[182]
Dosulepin	25 - 50	75	225	30.4 - 279	[182]
Desipramine	50 - 75	100 - 200	300	43 - 109	[182]
Trimipramine	75	150	300	N/A	[182]
Protriptyline	15	40	60	N/A	[182]
1.2. Selective Norepinephrine Reuptake Inhibitors or Tetracyclic Antidepressants*					
Maprotiline	25	25 - 75	150	100 - 400	[182]
2. Selective Monoamine Reuptake Inhibitors					
2.1. Selective Serotonin Reuptake Inhibitors					
Paroxetine	10	20	60	N/A	[182]
Sertraline	25 - 50	50	200	N/A	[182]
Fluvoxamine	50 - 100	100	300	N/A	[182]
Fluoxetine	20	20	60	N/A	[182]
Citalopram	10	20	40	47.5 – 116.6	[182]
Escitalopram	5 - 10	10	20	N/A	[182]
2.2. Selective Norepinephrine Reuptake Inhibitors					
Atomoxetine	40	80 - 100	100	N/A	[182]
Viloxazine	200	400	600	N/A	[182]
Reboxetine	4	8	10	N/A	[182]
Teniloxazine	N/A	N/A	N/A	N/A	N/A
2.3. Selective Dopamine and Norepinephrine Reuptake Inhibitors					
Bupropion	200	300	450		[182]

2.4. Selective Serotonin and Norepinephrine Reuptake Inhibitors					
Venlafaxine	75	150 - 225	375	N/A	[182]
Desvenlafaxine	50	50 - 100	400	N/A	[182]
Duloxetine	60	60 - 120	120	N/A	[182]
Milnacipran	50- 100	100	100	120 - 216	[182]
Levomilnacipran	20	40 - 120	120	N/A	[182]
Ansofaxin	N/A	N/A	N/A	N/A	N/A
Nefopam	20	120	120	N/A	[182]
C. Antidepressants with Predominant Effects on Receptor Systems					
1. Serotonin and alpha-2 adrenoceptor antagonists					
1.1 Antagonists of alpha-2-adrenergic receptors and 5-HT2a- and 5-HT3-receptors					
Mianserin	30	60 - 90	90	N/A	[182]
1.2. Antagonists of 5-HT2a and 5HT-2c Receptors and Alpha-2-Adrenergic Receptors					
Mirtazapine	15 - 30	15 - 45	45	N/A	[182]
1.3. 5-HT1a Receptor Agonist, 5-HT2a- and 5-HT2c-Receptor Antagonist and Alpha-1-Adrenergic Blocker					
Trazodone	75 - 100	75 - 150	600	N/A	[182]
1.4. 5-HT1a Receptor Partial Agonist with Serotonin Reuptake Inhibition					
Vilazodone	10	20 - 40	40	156	[182]
1.5. 5-HT2a and 5-HT2c receptor antagonist and Serotonin Reuptake Inhibitor					
Nefazodone	200	300 - 600	600	N/A	[182]
1.6. 5-HT1 Receptor Agonists					
Gepirone	N/A	N/A	N/A	N/A	N/A
Tandospirone	N/A	N/A	N/A	N/A	N/A
2. Melatonin MT1 and MT2 receptor agonist and Serotonin 5-HT2b and 5-HT2c receptor antagonist					
Agomelatine	25	25 - 50	50	N/A	[57]
D. Antidepressants Mixed (Multimodal), Other or Not Enough Learned Mechanism of Action					
2. Serotonin Reuptake Inhibitor and 5-HT1a Receptor Agonist, 5-HT1B Receptor Partial Agonist, 3. 5-HT3 Receptor Antagonist, 5-HT7 Receptor Antagonist					
Vortioxetine	10	20	20	9 - 18 - 33	[182]
2. S-Adenosylmethionine Derivative					
Ademetionine	500 - 1000	500 - 1500	1500	N/A	[57]
3. Facilitation of Serotonin Reuptake with Blockade of Its Destruction					
Tianeptine	12.5	25 - 50	50	N/A	[57]
4. Serotonin and Norepinephrine Reuptake Inhibitor and Serotonin Receptor Antagonist with Potent Antipsychotic Blockade of D2 Receptors					
Amoxapine	200	200 - 300	600	N/A	[182]

The interindividual variability of the effects can be explained by environmental, physiological and psychological factors, as well as concomitant diseases and the pharmacogenetic profile of a particular individual [142, 143]. According to experts, about a quarter of the total variability of the response to ADs is genetically determined [144]. Genes encoding target receptors for ADs are evolutionarily more conservative than genes encoding enzymes that metabolize ADs. Despite the fact that the available functional interpretation of the effects of major or minor allelic variants of target receptor genes can be used to personalize pharmacotherapy [145], the efficacy of pharmacodynamic genotyping is currently still questionable [146], in contrast to pharmacokinetic genotyping. Genes encoding enzymes responsible for the pharmacokinetics of ADs have a significant impact on the variability of the response and the effectiveness of blood pressure acting both on the

central nervous system [147], and on the heart [118]. Depending on the rate of drug metabolism, four pharmacogenetic phenotypes can be identified in patients receiving ADs: extensive metabolizer (EM); intermedium metabolizer (IM); poor metabolizer (PM); and ultrarapid metabolizer (URM) [148]. From the point of view of the problem of AD-induced QTc interval prolongation, individuals with the PM phenotype require special attention, since such patients may inadvertently have subtoxic or toxic levels of ADs in the serum. At the same time, such individuals are at high risk of QTc interval prolongation, especially against the background of chronic psychopharmacotherapy [28].

The development of panels for pharmacogenetic testing (PGx) and their active introduction into real clinical practice, which has been noted in recent years, confirm that the risk of an increase in ADs serum level is higher in patients with mental disorders having a pharmacogenetic profile PM [148]

Differences in plasma concentrations of ADs may be caused by polymorphisms in genes encoding cytochrome P450 isoenzymes (CYP), through which ADs are metabolized. The CYP superfamily is a class, containing heme-cofactor proteins that are predominantly localized in the liver. They are the main enzymes responsible for phase I of the oxidative reactions of many drugs and endogenous substances. More than 50 isoenzymes are known, the most significant of which are: CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. The metabolic activity of CYP is genetically determined, and allelic variants in the genes encoding CYP isoenzymes can lead to enzyme variants with higher, lower, or no activity. The prevalence of different genotypes and phenotypes varies markedly depending on the ethnicity of patients [149].

For example, the FDA warning for citalopram restricts the selection of a reduced dose for patients who are poor CYP2C19 metabolizers. The escitalopram label notes that patients who are poor CYP2C19 metabolizers may be exposed to supratherapeutic levels while taking the maximum recommended dose [104]. However, the use the PGx to determine the pharmacogenetic profile of patients with mental disorders is not currently standard clinical practice. The lack of such information may lead to the fact that empirical prescribing of ADs by psychiatrists without access to PGx, may expose some patients with poor metabolizers to an increased risk of AD-induced QT prolongation [101].

Also, the metabolism of ADs can be affected by alcohol intake, since the β-oxidation of alcohol is carried out with the participation of P450 isoenzymes of the liver, which leads to pharmacokinetic interactions with ADs [150, 151]. Smoking can also affect blood levels of ADs. Systematic review studies found evidence of reduced blood concentrations of fluvoxamine, duloxetine, mirtazapine and trazodone among smokers compared with non-smokers [152]. Blood levels of some ADs are known to be reduced in smokers due to induction of metabolism mediated by the enzymes CYP1A2 and CYP2B6 [153].

Table 5. General characteristics of the pharmacokinetics of antidepressants

Antidepressant	**Metabolic pathway**	**Key metabolic enzyme**	**Gene (OMIM Number)** [183]	**Single Nucleotide Polymorphism (RSID)**	**References**
A. Monoamine Oxidase Inhibitors					
1. Nonselective Irreversible Monoamine Oxidase Inhibitors					
Isocarboxazid	Hepatic				
Nialamide	N/A	N/A	N/A	N/A	
Tranylcypromine	Hepatic				
Phenelzine	Hepatic				
2. Selective Reversible Inhibitors Monoamine Oxidase Type A					

Pirlindole	Hepatic				
Moclobemide	Hepatic	Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[184, 185]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[184, 185]
3. Selective Reversible Inhibitors Monoamine Oxidase Type B					
Selegiline	Hepatic	Isoenzyme 2B6 of cytochrome P450	*CYP2B6* (123930)	*5A (rs3211371) *8 (rs12721655) *18 (rs28399499) *27 (rs36079186) *28 (rs34097093)	[185, 186]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[185, 186]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185, 186]
		Isoenzyme 3A5 of cytochrome P450	*CYP3A5* (605325)	*3 (rs776746) *6 (rs10264272) *7 (rs76293380)	[186 - 188]
B. Presynaptic Monoamine Reuptake Inhibitors					
1. Nonselective Presynaptic Monoamine Reuptake Inhibitors					
1.1 Tricyclic Antidepressants					
Amitriptyline	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 189, 190]
		Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513)	[149, 191, 192]

				*15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[185]
Imipramine	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 189]
		Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852)	[149, 185, 189]

				*17 (rs28371706)	
Clomipramine	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 189]
		Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
Pipofezine	Hepatic	Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[57, 191, 192]
Nortriptyline	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185]

		Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
Doxepin	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 189]
		Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685)	[185]

				*13 (rs72558187) *15 (rs72558190)	
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
Dosulepin	Hepatic	Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185]
		Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185]
Desipramine	Hepatic	Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511	[149, 191, 192]

				rs2470890) *16 (rs72547515 rs2470890)	
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
		Isoenzyme 2C19 of cytochrome P450 (demethylation)	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 189]
Trimipramine	Hepatic	Isoenzyme 1A2 of cytochrome P450 (demethylation)	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450 (demethylation)	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2D6 of cytochrome P450 (hydroxylation)	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 189]
Protriptyline	N/A	N/A	N/A		N/A
		1.2. Selective Norepinephrine Reuptake Inhibitors or Tetracyclic Antidepressants*			
Maprotiline	Hepatic				
		2. Selective Monoamine Reuptake Inhibitors			
		2.1. Selective Serotonin Reuptake Inhibitors			
Paroxetine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097)	[149, 185, 193]

				*4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 193]
Sertraline	Hepatic	Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[149, 185]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 193]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2B6 of cytochrome P450	*CYP2B6* (123930)	*5A (rs3211371) *8 (rs12721655) *18 (rs28399499) *27 (rs36079186) *28 (rs34097093)	[185, 193]
Fluvoxamine	Hepatic	Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513)	[149, 191, 192]

				*15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 193]
Fluoxetine	Hepatic	Isoenzyme 2C19 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[149, 185]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 193]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149]
Citalopram	Hepatic	Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 193]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759)	[149, 185]

				*20 (rs67666821)	
Escitalopram	Печеночный	Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[149, 185, 193]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
2.2. Selective Norepinephrine Reuptake Inhibitors					
Atomoxetine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185, 194]
Viloxazine*	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185]
Reboxetine	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
Teniloxazine	N/A	N/A	N/A		N/A
2.3. Selective Dopamine and Norepinephrine Reuptake Inhibitors					
Bupropion	Mixed (inclining hepatic)	Isoenzyme 2B6 of cytochrome P450	*CYP2B6* (123930)	*5A (rs3211371) *8 (rs12721655) *18 (rs28399499) *27 (rs36079186) *28 (rs34097093)	[149, 185]
2.4. Selective Serotonin and Norepinephrine Reuptake Inhibitors					
Venlafaxine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]

		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 193]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[185]
Desvenlafaxine**	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185, 195]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 195]
Duloxetine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 193]
		Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 193]

Milnacipran	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185]
		Isoenzyme 2C8 of cytochrome P450	*CYP2C8* (601129)	*2 (rs11572103) * 3 (rs10509681) (rs11572080) *4 (rs1058930)	[196, 197]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185]
		Isoenzyme 2J2 of cytochrome P450	*CYP2J2* (601258)	*2 (rs55753213) *3 (rs56307989) *4 (rs66515830) *6 (rs72547598)	[198]
Levomilnacipran	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs49863910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185, 199]
		Isoenzyme 2C8 of cytochrome P450	*CYP2C8* (601129)	*2 (rs11572103) * 3 (rs10509681) (rs11572080) *4 (rs1058930)	[196, 197, 199]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 199]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185, 199]
		Isoenzyme 2J2 of cytochrome P450	*CYP2J2* (601258)	*2 (rs55753213) *3 (rs56307989) *4 (rs66515830) *6 (rs72547598)	[198, 199]
Ansofaxine	N/A	N/A	N/A		N/A
Nefopam	N/A	N/A	N/A		N/A
C. Antidepressants with Predominant Effects on Receptor Systems					
1. Serotonin and alpha-2 adrenoceptor antagonists					
1.1 Antagonists of alpha-2-adrenergic receptors and 5-HT2a- and 5-HT3-receptors					

Mianserin	Hepatic				
1.2. Antagonists of 5-HT2a and 5HT-2c Receptors and Alpha-2-Adrenergic Receptors					
Mirtazapine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[149, 185, 200]
		Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
1.3. 5-HT1a Receptor Agonist, 5-HT2a- and 5-HT2c-Receptor Antagonist and Alpha-1-Adrenergic Blocker					
Trazodone	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
1.4. 5-HT1a Receptor Partial Agonist with Serotonin Reuptake Inhibition					
Vilazodone	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185, 201]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 201]
		Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185, 201]
1.5. 5-HT2a and 5-HT2c receptor antagonist and Serotonin Reuptake Inhibitor					

Nefazodone	Hepatic	Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[149, 185]
1.6. 5-HT1 Receptor Agonists					
Gepirone	N/A				
Tandospirone	N/A				
2. Melatonin MT1 and MT2 receptor agonist and Serotonin 5-HT2b and 5-HT2c receptor antagonist					
Agomelatine	Hepatic (90% CYP1A2 и 10% CYP2C9)	Isoenzyme 1A2 of cytochrome P450	*CYP1A2* (124060)	*1C (rs2069514) *1K (rs2069526 rs12720461 rs762551) *3 (rs56276455 rs2470890) *4 (rs72547516) *6 (rs28399424) *7 (rs56107638) *8 (rs72547517 rs2470890) *11 (rs72547513) *15 (rs72547511 rs2470890) *16 (rs72547515 rs2470890)	[149, 191, 192]
		Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[185]
D. Antidepressants Mixed (Multimodal), Other or Not Enough Learned Mechanism of Action					
1.	2. Serotonin Reuptake Inhibitor and 5-HT1a Receptor Agonist, 5-HT1B Receptor Partial Agonist, 5-HT3 Receptor Antagonist, 5-HT7 Receptor Antagonist				
Vortioxetine	Hepatic	Isoenzyme 2D6 of cytochrome P450	*CYP2D6* (124030)	*4 (rs3892097) *4F (rs3892097) *4G (rs3892097) *4H (rs3892097) *8 (rs5030865) *10 (rs1065852) *17 (rs28371706)	[185, 193]
		Isoenzyme 2C19 of cytochrome P450	*CYP2C19* (124020)	*2 (rs4244285) *4 (rs28399504) *5 (rs56337013) *8 (rs41291556)	[185, 193]
		Isoenzyme 3A4 of cytochrome P450	*CYP3A4* (124010)	*3 (rs4986910) *17 (rs4987161) *18 (rs28371759) *20 (rs67666821)	[185]
		Isoenzyme 3A5 of cytochrome P450	*CYP3A5* (605325)	*3 (rs776746) *6 (rs10264272)	[186 - 188]

			*7 (rs76293380)	
	Isoenzyme 2C9 of cytochrome P450	*CYP2C9* (601130)	*2 (rs1799853) *3 (rs1057910) *4 (rs56165452) *5 (rs28371686) *8 (rs7900194) *11 (rs28371685) *13 (rs72558187) *15 (rs72558190)	[185]
	Isoenzyme 2A6 of cytochrome P450	*CYP2A6* (122720)	*2 (rs1801272) *5 (rs5031017) (rs111033610) (rs28399447) *6 (rs4986891) *7 (rs5031016) *9A (s28399433) *11 (rs28399447) *17 (rs28399454) *18 (rs1809810) *19 (rs1809810) *23 (rs56256500) *24A (rs143731390) *24A (rs72549435) *26 (rs59552350) *26 (rs4986891) *27 (rs2839944) *27 (rs28399445) *35 (rs143731390) *41 (rs1404717037)	[185]
	Isoenzyme 2C8 of cytochrome P450	*CYP2C8* (601129)	*2 (rs11572103) * 3 (rs10509681) (rs11572080) *4 (rs1058930)	[196, 197]
	Isoenzyme 2B6 of cytochrome P450	*CYP2B6* (123930)	*5A (rs3211371) *8 (rs12721655) *18 (rs28399499) *27 (rs36079186) *28 (rs34097093)	[185]
2. S-Adenosylmethionine Derivative				
Ademetionine	Hepatic			
3. Facilitation of Serotonin Reuptake with Blockade of Its Destruction				
Tianeptine	Hepatic			
4. Serotonin and Norepinephrine Reuptake Inhibitor and Serotonin Receptor Antagonist with Potent Antipsychotic Blockade of D2 Receptors				
Amoxapine	Hepatic			

Note: * Also metabolized by conjugation mediated by isoforms of UGT (UGT1A9, UGT2B15) [202]

** Metabolized predominantly by conjugation mediated by isoforms of UGT (UGT1A1, UGT1A3, UGT2B4, UGT2B15 и UGT2B17) [195]

It is unrealistic to expect that practicing psychiatrists have the desire and ability to regularly study the scientific literature in addition to their clinical work. This partly

explains why it is necessary to translate reliable scientific evidence into informative clinical recommendations regarding the use of PGx to assess the risk of AD-induced QTc prolongation. Overall, there is a knowledge gap among clinicians in most parts of the world regarding the cost-effectiveness of predictive PGx in psychiatry, although a personalized approach in psychiatry could be cost-effective if PGx became less expensive. In addition, most existing cost-effectiveness models for PGx in psychiatry do not consider the indirect costs of correcting frequent and severe ADRs, which are known to be high for psychiatric patients. Although, in recent years, the cost of PGx has been decreasing, which makes it more likely that its results will be introduced into real psychiatric practice.

The simultaneous prescription of ADs with other psychotropic drugs (antipsychotics, mood stabilizers, anticonvulsants) is a common practice in the treatment of mental disorders. These concomitant drugs can affect the pharmacokinetics of ADs, which in turn contributes to the transformation of the pharmacogenetic profile of EM into the phenotypic URM, IM or PM (phenoconversion) due to their cumulative effect on the enzymatic activity of CYP isoenzymes (induction or inhibition, respectively). This phenoconversion may influence therapeutic response to an ADs and the risk of developing ADRs, including the risk of cardiotoxicity and AD-induced QTc prolongation. However, in most of the publications we analyzed, this problem was not considered. Although, we do not exclude that such studies could evaluate the adjusted risk of prolongation of the QTc interval during chronic psychopharmacotherapy prescribed in a polytherapy.

Although the results of genetic association studies convincingly demonstrate the role of the above-mentioned SNPs of the CYP family genes and the role of PGx in the promotion and safety of ADs. There are no large-scale (multicenter) international studies devoted to the cost-effectiveness of introducing PGx into real clinical practice in psychiatry. Although dosing recommendations for many psychotropic medications, including ADs, are being developed based on PGx results, the majority of ADs are prescribed to patients with psychiatric disorders who have not undergone predictive PGx and/or genetic screening [154] (for example, monogenic and multifactorial forms of LQTS) before or at the beginning of treatment, even in identifying QT interval prolongation at the start of pharmacotherapy.

Therapeutic drug monitoring (TDM) of plasma levels of ADs has been used in psychiatry for a long time, particularly for TCAs [60]. This diagnostic method takes into account all factors of interindividual variability in the metabolism of ADs and other drugs. However, PGx can be performed before ADs are prescribed, whereas TDM can only be performed when ADs levels reach a stable level and when the patient may already have AD-induced QTc prolongation. Therefore, ideally, the psychiatrist should consider all available genetic, physical, dietary, and environmental parameters to make the best possible choice of ADs and dosage when initiating therapy for each individual patient. Once the level of ingested ADs reaches a stable blood level, TDM may be useful to clarify whether the QTc prolongation is due to disruption of the pharmaconetics of ADs and its accumulation [144].

Ideally, PGx-based decision-making algorithms for the mental health practitioner should include information on a wide range of genetic, pharmacokinetic, and environmental factors associated with the risk of developing AD-induced QTc prolongation. This is a pressing interdisciplinary problem in psychiatry, since many of the most reliable predictors of the risk of AD-induced prolongation of the QTc interval may be not only clinical, but also psychosocial in nature [155].

However, most psychiatrists express the opinion that it is advisable to prescribe PGx to patients with mental disorders in cases of development of ADRs, including cardiotoxic ones, followed by pharmacogenetic counseling [156, 157]. At the same time, the developers of PGx panels support the predictive use of this diagnostic method (that is, before prescribing ADs) [158].

The reality is that the evidence base for both proactive and reactive use of PGx to predict and diagnose AD-induced QTc prolongation ADRs remains limited.

Various decision systems are available to clinicians when choosing a PGx. One of the most well-known system is the Oxford Center for Evidence-Based Medicine (CEBM) level of evidence [159], which can help clinicians identify and assess the risks of ADs use [155] [158, 160, 161]. The CEBM recommends consider at least four questions before deciding to use ADs: (1) "Is there good reason to believe that the patients observed are sufficiently similar to the patients in the randomized clinical trials? (randomized clinical trials on the treatment of depression mainly involved white women over the age of forty who had no comorbidities [160], with underrepresentation of patients of non-Caucasian origin, and the allelic frequency of genes encoding key enzymes of ADs metabolism used to assess the pharmacogenetic profile varies significantly in frequency depending on ethnic origin) [162-164]; (2) «Does the PGx panel have clinically significant benefits that outweigh the harms?" (Evidence to date suggests the potential benefits associated with the use of PGx and adoption support systems [165] [166] [167], such as reduction of ADRs [165] [168] and cost saving [165, 169-171]). The exception is a long period of time (from 1 day to 3 weeks) to obtain the results of PGx in cases where a delay in initiating the prescription of ADs may be undesirable from a bioethical and clinical point of view [172], as well as the potential risk of violation of genetic confidentiality [173, 174]; (3) "Is another tool better than PGx?" (there are no large comparative studies of the effectiveness of PGx panels and decision support systems); (4) "Are the patient's values and circumstances compatible with the use of PGx decision support tools?" (understanding of the value of PGx panels may vary from patient to patient [174, 175].

Discussion

This narrative review updates our knowledge of AD-induced QT interval prolongation in patients with mental disorders. Single studies of the effect of MAOIs on the duration of the QTc interval can be explained by the rarity of the use of these ADs in real clinical practice due to the high risk of developing ADRs (primarily hepatotoxicity, tyrosine syndrome), which leads to the gradual phase-out of some ADs of this group, and, accordingly, low interest in them from scientists and practitioners.

Most ADs of the non-selective monoamine reuptake inhibitor subgroup, except for dosulepine, have a dose-dependent effect, that is, the duration of the QTc interval depends on the serum level of the drug according to therapeutic drug monitoring [86]. Therapeutic doses of ADs of this subgroup can cause prolongation of the QTc interval to borderline values, very rarely causing the development of TdP and SDS. At toxic doses, TCAs cause a significant prolongation of the QTc interval. Patients taking TCAs and having an underlying conduction defect, especially the blockade of the bundle of His bundle, are at increased risk of developing symptomatic atrioventricular block [60]. Accordingly, the appointment of TCAs is undesirable for patients with impaired conduction, especially at high doses [60].

Among SNRIs, venlafaxine and its metabolite desvenlafaxine have the greatest risk of prolongation of the QTc interval, TdP, and SDS. Other ADs of this class do not cause significant prolongation of the QTc interval.

Among SSRIs, citalopram clearly has the highest risk of QTc prolongation. A slightly lower risk, but also high, escitalopram has. According to the present review, sertraline is not a safe AD in terms of QTc interval prolongation and development of TdP. When taking paroxetine and fluoxetine, the risk of prolongation of the QTc interval is low. In relevant studies, QTc prolongation was rare and non-significant. Probably the safest SSRI is fluvoxamine. We did not find a single study demonstrating a prolongation of the QTc interval when taking this AD.

The high risk of developing TdP in elderly patients when taking citalopram conflicts with the ability of citalopram to improve cognitive functions [176, 177] and to stop non-cognitive impairments, in particular, agitation, in patients with dementia of the

Alzheimer's type [106]. This may create certain difficulties for a psychiatrist in the selection of therapy for a particular patient of an older age group.

The effect of AD-induced sodium channel blockade on QTc interval prolongation is interesting. Among SSRIs, sodium channel blockers are paroxetine, fluoxetine, and fluvoxamine [65]. Paroxetine, by inhibiting sodium Nav1.5 channels, significantly reduces the fast sodium current in human left ventricular cardiomyocytes, thereby slowing down conduction and reducing their excitability [92]. At the same time, sertraline, citalopram and escitalopram do not block sodium channels [65]. However, citalopram, escitalopram and sertraline prolong the QTc interval to a much greater extent, unlike paroxetine and fluvoxamine. The mechanism of this phenomenon needs further study. Also, ADs with sodium channel blocking properties did not show a higher incidence of SDS compared with ADs without this property (OP 0.96 [95% CI 0.89–1.05]) [65].

A similar paradoxical situation arises when studying the effect of duloxetine and venlafaxine on the QTc interval. Duloxetine, which is a strong inhibitor of the sodium Nav1.5 channel in vitro, unlike venlafaxine, does not affect the duration of the QTc interval, being probably one of the safest ADs in this respect.

Stoetzer et al. [33] suggest that this effect may be due to the strong binding of duloxetine to plasma proteins, which leads to low effective concentrations *in vivo* and does not cause a corresponding inhibition of sodium channels. At the same time, the authors themselves note a contradiction in the case of amitriptyline, which also binds strongly to plasma proteins, but has a dose-dependent prolongation of the QTc interval. Amitriptyline is known to inhibit cardiac hERG channels with a significantly higher affinity than duloxetine. In this regard, the authors conclude that hERG channel inhibition may be more important for QTc prolongation than Nav1.5 inhibition [33]. Finally, an increased risk of SDS was found in patients taking ADs that inhibit cardiac potassium channels, but not ADs that inhibit voltage-dependent sodium channels [65].

The effect of enantiomers on the racemate is interesting. Henry et al. [178] compared the pharmacokinetics of the fluoxetine's R-enantiomer and the racemate and found differences in QTc effects between the two enantiomers. The FDA also presented 2 similar studies of QTc prolongation with citalopram and escitalopram in a recent warning about citalopram [104]. Even though escitalopram is the S-enantiomer of citalopram, the QT prolonging effects of escitalopram are not mentioned in the FDA warning (although other agencies do it) [104, 179].

Most of the information analyzed in this review was obtained from retrospective studies [52, 70-72, 80, 126]. Prospective studies [74], especially consistent with level A evidence [102], have been sporadic. Studies rarely analyzed risk factors for QTc and TdP prolongation, such as age, gender, cardiovascular disease, and concomitant therapy. Information on duration of therapy, comorbidities, and general somatic examination of patients, such as serum electrolyte levels, was rarely present. Patient compliance and potentially confounding factors, such as smoking [107] and the pharmacogenetic profile of patients, including genetic variants that can alter the effect of ADs on the QTc interval, have not been taken into account anywhere [44].

Okayasu et al. believed that the difference in the results of assessing the risk of SDS when taking various ADs may be associated with the ethnicity of patients [73]. Despite the declaration of ethnic and racial diversity in some studies, none of them evaluated the dependence of QTc prolongation on the race and/or ethnicity of patients with mental disorders. Thus, it is maximally generalized the groups, standardizing the selection of ADs and their doses, and minimizing mimicking the personification of therapy [44, 71, 93].

At the same time, to reduce the risk of AD-induced TdP, the following recommendations were formulated: 1) avoid prescribing ADs that prolongs the QTc interval to patients with a QTc interval > 450 msec before treatment; 2) stop taking ADs that prolongs the QTc interval, if the QTc interval is extended to 500 msec or more after the start of therapy; 3) reduce the dose or stop taking ADs that prolongs the QTc interval if the QTc interval increases by 60 msec or more compared to the value before treatment; 4) maintain the

concentration of potassium, magnesium and calcium in the blood serum within the normal range; 5) avoid the use of ADs that prolong the QTc interval in patients with heart failure and left ventricular ejection fraction <20%; 6) avoid important drug-drug interactions that increase the risk of prolongation of the QTc interval; 7) adjust doses of renally excreted ADs that prolong the QTc interval in patients with acute kidney injury or chronic kidney disease; 8) avoid rapid intravenous administration of ADs that prolongs the QTc interval; 9) avoid the simultaneous use of more than one AD that prolongs the QTc interval; 10) avoid the use of ADs that prolongs the QTc interval in patients with a history of drug-induced TdP or in those who have previously been resuscitated after an episode of SDS; 11) avoid prescribing ADs that prolongs the QTc interval in patients with one of the congenital/familial long QT syndromes [31].

Conclusions

The use of ADs requires a personal assessment of the risk of QTc and TdP prolongation to achieve an optimal balance between the efficacy and safety of psychopharmacotherapy and minimize the risk of potentially fatal complications. It should be recognized that there is not yet enough evidence base for the widespread introduction of ADs' pharmacogenetics into everyday psychiatric practice in patients with mental disorders for personalized risk assessment of AD-induced cardiotoxic ADRs. However, increasing the level of knowledge of practicing psychiatrists is essential so that they are adequately educated in the field of modern advances in the pharmacokinetics and pharmacogenetics of ADs and are provided with adequate guidelines for the clinical interpretation of TDM and PGx results to assess risk of QTc interval prolongation in an individual patient.

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