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Article

A Sociological Study of Awareness of Practitioning Physicians about the Cardiosafety of Antidepressants

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Abstract: Prediction and prevention of cardiotoxic adverse reactions in neurological diseases is a pressing issue due to necessity for long-term use of antidepressant drugs. **The aim** of the study was to examine the quantity of antidepressant prescriptions, observation of adverse events (especially cardiovascular ones) and the caution in prescribing by practicing neurologists compared with physicians of other specialties. **Materials and methods:** 97 physicians of various specialties participated in the survey. After excluding physicians who did not use antidepressants in their practice, the participants were divided into two groups: neurologists and physicians of other specialties. Differences in responses between the two groups were assessed with the Pearson chi-square test ($\chi 2$) and the Kruskal-Wallis test. **Results**. The analysis of a survey of physicians using antidepressants in their clinical practice revealed the statistically significant differences between neurologists and physicians of other specialties who participated in the study. Neurologists tend to underestimate the cardiotoxicity of antidepressant medications (particularly SSRIs), which can lead to a potentially fatal complication—ventricular tachycardia (Torsade de Pointes). A statistically significant difference in awareness of the diagnostic criteria for long QT syndrome was found in medical practice of neurologists and physicians in other specialties. **Conclusion.** As a result of the analysis the obtained results, the following ways of improving the dispensary observation of patients on antidepressants were: increasing awareness and alertness of practicing physicians about the long QT syndrome; ECG monitoring before and during taking antidepressants; collection of family history and life history in patients before prescribing antidepressants. Presence of tachycardia, syncope, or anoxic seizures in a patient taking antidepressants can arise suspicion for TdP, a potentially fatal complication of QT syndrome; it requires immediate discontinuation of the drug, replacement with a less cardiotoxic one, 24-hour Holter ECG monitoring, and pharmacogenetic testing.

Keywords: *antidepressants; selective serotonin reuptake inhibitors; cardiosafety; circumspection; adverse drug reactions; long QT syndrome.*

1. INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) have a wide therapeutic range, they are relatively easy to prescribe, with minimal need for dose adjustment (with the excep-

tion of fluvoxamine). SSRIs have some anticholinergic, adrenolytic, and cardiotropic effects [1]. In recent years, SSRIs have been increasingly used in neurology. SSRIs have been proposed as an alternative treatment for chronic pain due to the fact that they are better tolerated and cause fewer adverse reactions (ARs) than tricyclic antidepressants. Nevertheless, long-term SSRIs (for example, with chronic pain syndrome [2]) increase the risk of adverse drug reactions (ADRs), including sexual dysfunction, weight gain, gastrointestinal disorders, serotonin syndrome. Some SSRIs can lead to serious drug interactions [3].

SSRIs are a cornerstone in the treatment of various neurological diseases and psychiatric disorders, demonstrating effectiveness in the treatment of conditions such as chronic pain syndromes, tension headaches, neuropathies and the early recovery period after a stroke. However, despite their therapeutic benefits, long-term use of SSRIs is associated with potential ADRs, including cardiovascular risks, metabolic changes, and serotonin syndrome. Drug-induced prolongation of the QT interval can be potentially fatal, leading to an increased risk of ventricular tachycardia, known as Torsades de Pointes (TdP) [4, 5]. Neurologists have low confidence in early detection of SSRI-induced QT prolongation, despite the fact that some antidepressants in this class (e.g., escitalopram) have a high risk of developing this potentially fatal adverse reaction [6].

The purpose of the study: to investigate the frequency of prescribing various SSRIs by neurologists and related specialists in real clinical practice; o study the degree of awareness of specialists (neurologists, general practitioners, internists, psychiatrists and doctors of other clinical specialties) about the risk of potentially life-threatening ADRs of antidepressants.

2. MATERIAL AND METHODS

The study was carried out on the basis of the Institute of Personalized Psychiatry and Neurology of the V. M. Bekhterev National Medical Research Centre for Psychiatry and Neurology. The study included 97 participants physicians**:** 41 (41.8%) neurologists, 56 (58.2%) physicians of other specialties. Criteria for inclusion in the main group: clinical practice as a doctor of a therapeutic specialty; completed higher education in the specialty programs "Medical Science" or "Pediatrics"; practical activity on the territory of the Russian Federation (citizenship of the Russian Federation). Exclusion criteria from the main group: medical activity exclusively in positions of doctors of diagnostic and surgical specialties; teachers of medical universities who do not practice medicine; students who do not have a diploma of higher medical education; foreign citizenship.

To obtain information on the main formal sociometric data, the subjects were asked to conduct a questionnaire using the author's Yandex Forms questionnaire (https://forms.yandex.ru/u/664deffdeb61461c2fb7cd76/), which included the following questions: age; level of education, length of service; format of clinical activity, specialization; place of work; for which diseases the subject prescribes antidepressants, SSRIs; the most cardiosafety groups of antidepressants, individual SSRIs; the most common antidepressant ADRs found in clinical practice; methods of preventing ADRs when prescribing antidepressants.

Statistical analysis of the results of the clinical part of the study was carried out using the Jamovi v. 2.6.44 program (JASP, Europe) using descriptive statistics methods. The critical significance level (p) was assumed to be 0.05.

3. RESULTS

3.1. General characteristics of the participants

97 people have participated in the study (practicing neurologists, doctors of related specialties). A survey of 97 specialists was conducted: 41 neurologists (41.8%), 56 physicians of other clinical specialties (58.2%). The age of the survey participants (N = 97) ranged from 24 to 74 years. The average age was 38.3 (standard deviation (sd) ± 13.1); median (Me) = 35.0 years.

Thus, two groups were formed. Group 1 (main group) consisted of 41 neurologists (42.3%). Group 2 (comparable) consisted of 56 physicians of other specialties (57.7%), of whom 14 (25%) were psychiatrists and 42 (75%) were internists and general practitioners. The sample consisted of physicians with different working conditions (outpatient, inpatient, academic) and an average medical experience of 13.6 years, with no significant differences in professional qualifications between the groups. The distribution of specialists by workplace (N = 97) was as follows: outpatient admission — 35 (36.1%); hospital work — 28 (28.9%); outpatient and inpatient work – 6 (4 neurologists, 2 specialists of other profile) – 6.2%; and 28 participants indicated research centers and/or higher education institutions as their place of work (28.9%). The average medical experience was 13.6 (± 13.0); Me 10.0 years. The minimum length of service was up to 1 year, and the maximum was 50 years.

Among neurologists, the average medical experience was 14.8 (± 12.4) years; Me 10.0 years. The minimum length of service was up to 1 year, and the maximum was 42 years. Among doctors of other specialties, the mean medical experience was 12.6 (± 13.5) years; Me 5.5 years. The minimum length of service was up to 1 year, and the maximum was 50 years. There were no statistically significant differences in medical experience in the main and comparable groups (p-value > 0.005).

In the group, 1 participant (2%) indicated that he did not prescribe antidepressants in his clinical practice, and therefore 40 questionnaires were included in further statistical processing. In the group 2, 12 participants indicated that they do not prescribe antidepressants in their clinical practice, and therefore 44 questionnaires were included in further statistical processing. Thus, 84 questionnaires (N = 84) were included for subsequent statistical processing.

Group 1 consisted of 40 neurologists (47.6%). Group 2 consisted of 44 physicians of other specialties (52.4%). When examining the characteristics of professional activity, there were no statistically significant differences in qualifications (p-value > 0.05): medical experience (years), qualification category and academic degree (p-value > 0.05). A total of 10 doctors of medical sciences (11.9%) and 14 candidates of medical sciences (16.7%) participated in the study.

Statistically significant (p-value < 0.05) were differences in the age of patients supervised by specialists: 35% of neurologists (group 1) mainly lead children and adolescents in their clinical practice, physicians of other specialties less often lead children's practice (2.3% treat children and adults, 9.1% treats only children), which may affect the results of the study due to the limited number of SSRIs officially allowed in pediatric practice in Russia (sertraline and fluvoxamine [7]). To summarize, after excluding doctors who do not actively prescribe antidepressant drugs (1 neurologist and 12 other physicians), the questionnaire analysis was reduced to 84 participants. Despite the statistically confirmed absence of a significant difference in the experience and qualifications of the respondents, there was a noticeable difference in the demographic characteristics of the patients supervised by the study participants: neurologists treated children and adolescents much more often (9.1%) compared with other specialists (2.3%), which may affect the prescribing patterns and awareness of practitioners, given the limited number of the number of SSRIs approved for use in pediatrics (sertraline and fluvoxamine).

3.2. Research of the experience of using antidepressants in real clinical practice

The surveyed specialists answered a set of questions on the use of antidepressants in real clinical practice for a comparative analysis of the experience of prescribing this group of drugs.

According to the frequency of use of antidepressants, 3 groups are identified (Table 1): prescribers up to 1 time per day, prescribers up to 1 time per week, prescribers less than 1 time per month. There was no statistically significant difference in these groups (p-value > 0.05), which indicates approximately the same frequency of use of antidepressants in real clinical practice. However, if psychiatrists are excluded from the group of physicians of other specialties (13 participants), statistically significant differences were found (p-value = 0.001), which is associated with less use of antidepressants by doctors of other specialties.

Table 1. Characteristics of observation groups depending on the frequency of antidepressant prescription

How often do you prescribe antidepressants?	Group 1 (neurologists)			Group 2 (physicians of other specialties)		
	n	%	Accumulated %	n	%	Accumulated %
I prescribe up to 1 time per day	6	15.0%	15.0%	5	11.4%	11.4%
I prescribe up to 1 time per week	16	40.0%	55.0%	12	27.3%	38.6%
I prescribe it less than once a month	18	45.0%	100.0%	27	61.4%	100.0%

The frequency of use of certain groups of antidepressants has been investigated. The results of the survey showed that doctors of all specialties most often use tricyclic antidepressants (TCAs), SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) in their practice (Table 2, Figure 1). The difference in the use of SNRIs (milnacipran, duloxe-

tine, venlafaxine) was statistically significant (p-value = 0.002). This group of antidepressants is much more often prescribed by neurologists. TCAs are also more often used by neurologists, and SSRIs by doctors of other specialties, but no statistically significant difference was found (p- value = 0.093 and p-value = 0.821, respectively). NRIs (atomoxetine) and serotonin and adrenergic alpha-2 receptor antagonists (mianserin, mirtazapine) are less commonly prescribed.

Table 2. Characteristics of the frequency of prescription of antidepressants of various pharmacological groups

Antidepressant group	**Neurology, n/%**	**Other specialties, n/%**	**Total participants, N/%**
TCA	19/47.5%	13/29.5%	32/38.1%
SSRI	31/77.5%	34/77.3%	65/77.4%
SNRI	20/50%	8/18.2%	28/33.3%
NRI	1/2.5%	2/4.5%	3/3.6%
Serotonin and alpha-2-adrenergic receptor antagonists	2/5%	2/4.5%	4/4.8%
Serotonin receptor antagonists and agonists	4/10%	5/11.4%	9/10.7%
Multimodal action	9/22.5%	5/11.4%	14/16.7%
Others (agomelatine, ademetionine)	3/7.5%	7/15.9%	10/11.9%

Note: *TCA - tricyclic antidepressants; SSRI - selective serotonin reuptake inhibitors; SNRI - serotonin–norepinephrine reuptake inhibitors; NRI - noradrenaline reuptake inhibitor.*

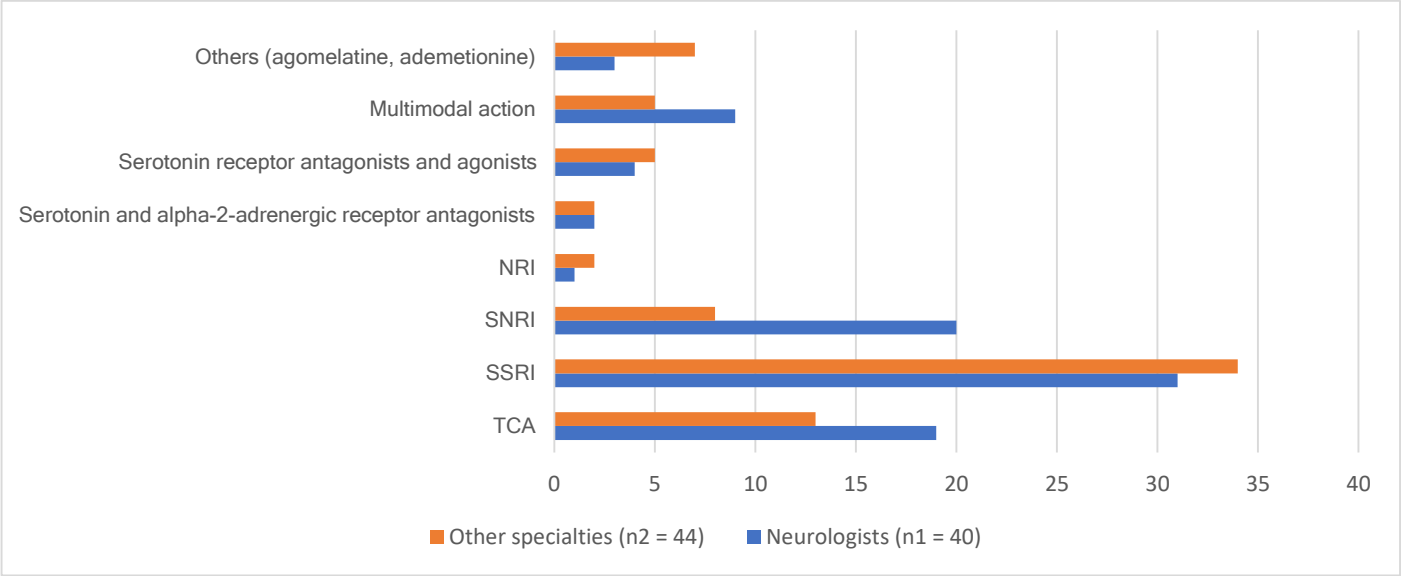

Figure 1. Absolute frequency of prescription of antidepressants of various pharmacological groups by neurologists and physicians of other specialties. ***Note:*** *TCA - tricyclic antidepressants; SSRI - selective serotonin reuptake inhibitors; SNRI - serotonin–norepinephrine reuptake inhibitors; NRI - noradrenaline reuptake inhibitor.*

3.1. Study of indications for prescribing antidepressants in real clinical practice

The next block of questions was devoted to clinical cases faced by doctors of various specialties. Several possible answers were suggested, including the following indications for prescribing antidepressants (Table 3).

Table 3. Conjugation table with calculation of χ^2 n1 and n2 according to antidepressant indications.

In what cases do you prescribe antidepressants?	Specialty		Total participants, N	χ^2	df (degrees of freedom)	p-value
	Other specialty, n	Neurology, n				
Anxiety disorders	32	32	64	0.611	1	0.434
Depression, depressive syndrome	32	32	64	0.611	1	0.434
Primary headache	6	20	26	13.0	1	<0.001
Chronic pain syndrome (dorsopathy, painful form of polyneuropathy)	22	34	56	11.6	1	<0.001
Sleep disorders	22	21	43	0.0524	1	0.819
Chronic fatigue syndrome	2	3	5	0.327	1	0.568
Cognitive disorders	1	4	5	2.23	1	0.135
Eating disorders (bulimia, anorexia)	9	4	13	1.75	1	0.186
Functional dyspepsia, irritable bowel syndrome	12	2	14	7.48	1	0.006

The results of the statistical analysis of this block of the questionnaire demonstrated the expected results. There were statistically significant differences in the prescribing of antidepressants for primary headache (tension-type headache, cluster headache, migraine) and chronic pain syndrome (dorsopathy, painful polyneuropathy). In these diseases, neurologists were more often prescribed antidepressants (p-value < 0.05). Physicians of other specialties were significantly more likely to prescribe antidepressants for functional dyspepsia and irritable bowel syndrome (p-value < 0.05).

Most of the participants in this study prescribe antidepressants for a long time (Table 4): 6 (7.14%) participants < 1 month, including group 1 - 3 (7.5%), group 2 - 3 (6.8%); 28 (33.33%) participants are prescribed antidepressants from 1 to 3 months, including group 1 - 14 (35.0%), group 2 - 14 (31.8%); 50 (59.52%) participants prescribe antidepressants to their patients for a period of > 3 months: group 1 - 23 (57.5%), group 2 - 27 (61.4%). There was no statistical difference in the duration of antidepressant prescribing between the two groups of physicians (p-value > 0.05).

3.2. Study of the caution of practitioners about the development of adverse drug reactions caused by taking antidepressants in real clinical practice

The next block of questions was devoted to adverse drug reactions (ADRs), which doctors of various specialties face most often in their clinical practice. It was suggested to note several possible answers, among which the following ADRs were indicated, divided by organ system (Table 5).

Table 4. Conjugation table for the duration of the prescribed course of antidepressants.

What is the average duration of the antidepressant therapy you prescribed?	Specialty		Total participants, N
	Other specialty, n	Neurology, n	
1-3 months	14	14	28
More than 3 months	27	23	50
Up to 1 month	3	3	6
Total	44	40	84

Table 5. Conjugation table (Kruskal-Wallis test) for adverse reactions of antidepressants that the physician encountered most often in practice.

What adverse reactions to antidepressants do your patients most often experience?	Specialty		Total participants, n/%	χ^2	df	p-value
	Other specialty, n/%	Neurology, n/%				
From the central nervous system (dizziness, headache, convulsions)	19/43.2%	20/50%	39/46.4%	0.392	1	0.531
From the gastrointestinal tract (dyspepsia, bowel disorder, nausea and vomiting)	16/36.4%	15/37.5%	31/36.9%	0.116	1	0.914
From the cardiovascular system (arterial hypo- and hypertension, tachycardia and bradycardia, changes in ECG, postural hypotension)	9/20.5%	7/17.5%	16/19.0%	0.119	1	0.731
From the mental sphere (sleep disturbance, anxiety, akathisia, suicidal thoughts, asthenia)	10/22.7%	18/45%	28/33.3%	4,6216	1	0.032
From the endocrine system (changes in body weight, edema, effects on libido, hypo- and hyperglycemia)	6/13.6%	10/25%	16/19.0%	1.75	1	0.185
Impaired visual function	0	0	0	ND	ND	ND
Impaired hearing function	0	0	0	ND	ND	ND
Hematological disorders (abnormal bleeding)	0	0	0	ND	ND	ND
Allergic reactions	3/6.8%	4/10%	7/8.3%	0.278	1	0.598
There were no adverse reactions	13/29.5%	8/20%	21/25%	1.02	1	0.313

Participants could mark at least several options, including the option "*There were no adverse reactions*." The subjects were least likely to experience pathological bleeding while taking antidepressants, ARs from the organs of vision, and hearing functions. Most often, participants recorded: ADRs from the central nervous system: group 1 – 20 (50.0%), group 2 – 19 (43.2%); ADRs from the gastrointestinal tract: group 1 – 15 (37.5%), group 2 – 16

(36.4%); affects the psychic sphere: group 1 – 18 (45.0%), group 2 – 10 (22.7%). There were statistically significant differences in the observation of ADRs from the mental sphere (sleep disorders, anxiety, akathisia, suicidal thoughts, asthenia), which neurologists recorded significantly more often than doctors of other specialties (p-value < 0.05).

Also, 19% participants included in the sample (7 neurologists and 9 doctors of other specialties) noted frequent ADRs from the cardiovascular system. At the same time, 50% (17 (38.6%) physicians of other specialties and 25 (62.5%) neurologists) noted in the following question that they had not encountered cardiovascular ADRs while taking antidepressants in their clinical practice (Tables 6 and 7). Statistically significant differences were revealed between the responses of these groups: thus, neurologists were much less likely to register prolongation of the QT interval, tachycardia and arterial hypotension, but more often arterial hypertension and bradycardia (p-value < 0.05). Most often, on the part of the cardiovascular system while taking antidepressants, doctors of all specialties observed tachycardia (22.6%) and arterial hypotension (13.1%).

Table 6. Cardiovascular adverse drug reaction

What adverse cardiovascular reactions did your patients experience most often?	Specialty		Total participants, N/%
	Other specialty, n/%	Neurology, n/%	
Patients did not experience any adverse reactions.	17/38.6%	25/62.5%	42/50.0%
Arterial hypertension	0	2/5.0%	2/2.4%
Arterial hypotension	8/18.2%	3/7.5%	11/13.1%
Bradycardia	0	3/7.5%	3/3.6%
Postural arterial hypotension	2/4.5%	1/2.5%	3/3.6%
Tachycardia	13/29.5%	6/15.0%	19/22.6%
QT prolongation	4/9.0%	0	4/4.8%
Total	44/100%	40/100%	84/100%

Table 7. Comparison of adverse cardiovascular event detection (χ^2 test)

	Meaning	df (degrees of freedom)	p-value
χ^2	15.6	6	0,016
N	84		

Table 8. Conjugation table of the most dangerous adverse drug reactions of antidepressants

Which adverse reaction do you consider to be the most serious?	Specialty		Total participants, N/%	χ^2	df (degrees of freedom)	p-value
	Other specialty, n/%	Neurology, n/%				
Serotonin syndrome	23 /52.3%	20 /50.0%	43 /51.2%	0.0433	1	0.835
Neuroleptic malignant syndrome	21 /47.7%	24 /60.0%	45 /53.6%	1.27	1	0.260
Long QT syndrome and TdP	33 /75.0%	24 /60.0%	57 /67.9%	2.16	1	0.142
Arterial hypertension	0	8 /20.0%	8 /9.5%	9.73	1	0.002
Arterial hypotension	1/2.3%	11 /27.5%	12 /14.3%	10.9	1	<0.001

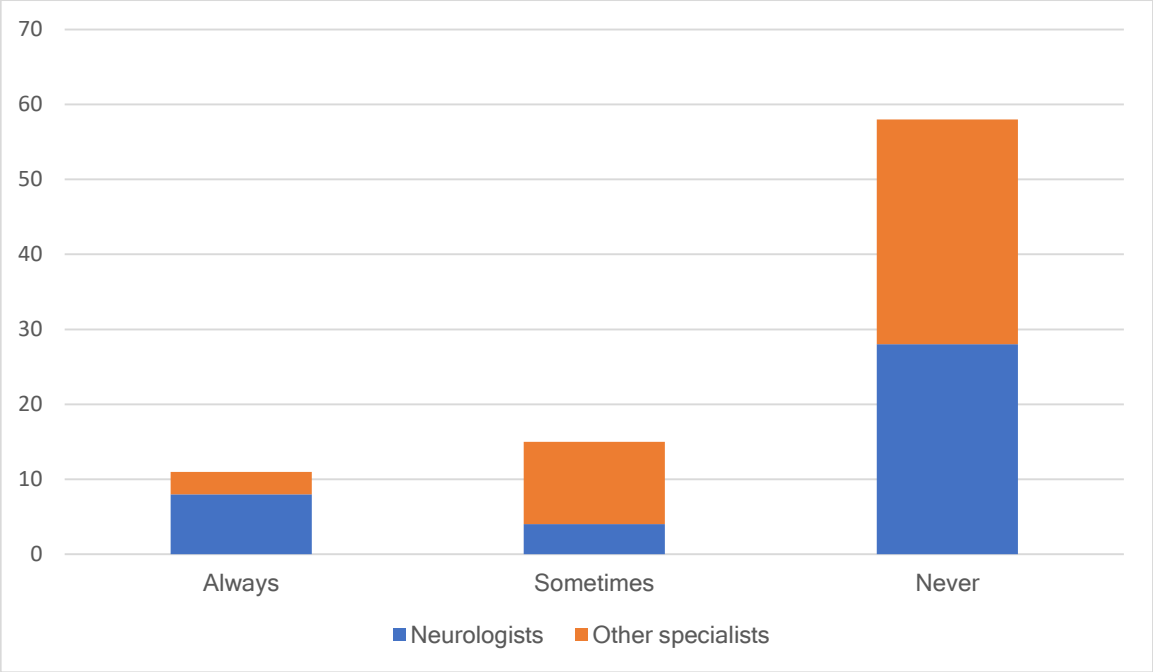

Figure 2. Frequency of filling out adverse drug reaction report cards by neurologists and physicians of other specialties.

When we asked about the most serious ADRs while taking antidepressants, the respondents were asked to choose several options from the following life-threatening conditions (Table 8).

The calculation showed a statistically significant difference in these groups (p-value < 0.05): neurologists more often noted hypotension and hypertension as the most life-threatening conditions caused by taking antidepressants. A study of the frequency of participants filling out notification cards for antidepressant-induced ADRs (Figure 2) showed no statistically significant difference: neurologists (70%) and physicians of other specialties (68%) do not fill out notification cards, which leads to a distortion of the results of monitoring the safety of this group of drugs in the Russian Federation.

3.3. Study of alertness for the development of antidepressant-induced cardiovascular adverse drug reactions in real clinical practice

A block of questions devoted to the study of participants' alertness to the development of antidepressant-induced cardiovascular disorders demonstrated that only 15% do not prescribe ECG to patients before taking antidepressants, 34.5% (37.5% neurologists and 34% physicians of other specialties) participants prescribe ECG to patients situationally, and 50% of all participants (42.5% neurologists and 56.8% physicians of other specialties) always prescribe an ECG to patients before taking antidepressants. Thus, there were no statistically significant differences in adherence to ECG prescribing for monitoring antidepressant-induced cardiac arrhythmias (p-value > 0.05). The proportion of participants prescribing ECG to patients while taking antidepressants turned out to be even lower: 26% participants (30% neurologists and 22.7% physicians of other specialties, p-value > 0.05) do

not show alertness to the development of prolonged long QT syndrome on the background of prolonged use of antidepressants.

Next, the r participants were asked to select the most dangerous and safest groups of antidepressants in relation to cardiotoxicity (Tables 9 and 10). As a result, no statistically significant differences were found between the two groups of study participants. The participants considered the following groups of drugs to be the safest antidepressants (in descending order): SSRIs (paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, fluoxetine), SNRIs (milnacipran, duloxetine, venlafaxine), multimodal antidepressants (vortioxetine). TCAs (amitriptyline, clomipramine, imipramine, pipofezine) were identified as the most dangerous group of antidepressants, 80.9% of all respondents noted this group as the most cardiotoxic.

Table 9. Safety contingency table for different groups of antidepressants (Kruskal-Wallis test)

Which groups of antidepressants do you think are the SAFER in terms of cardiotoxicity?	**Specialty**		**Total participants, N/%**	χ^2	**df (degrees of freedom)**	**p-value**
	Other specialty, n/%	**Neurology, n/%**				
TCAs (amitriptyline, clomipramine, imipramine, pipofezine)	3/6.8%	6/15.0%	9/10.7%	1.47	1	0.226
SSRIs (paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, fluoxetine)	33/75.0%	24/60.0%	57/67.9%	2.16	1	0.142
sNRIs (milnacipran, duloxetine, venlafaxine)	11/25.0%	12/30.0%	2327.4%	0.263	1	0.608
SNRI (atomoxetine)	2/4.5%	2/5.0%	4/4.8%	0.00955	1	0.922
Serotonin and alpha-2-adrenergic receptor antagonists (mianserin, mirtazapine)	4/9.1%	3/7.5%	7/8.3%	0.0694	1	0.792
Serotonin receptor antagonists and agonists (trazodone)	6/13.6%	1/2.5%	7/8.3%	3.40	1	0.065
Serotonin and alpha-2-adrenergic receptor antagonists (mianserin, mirtazapine)	4/9.1%	3/7.5%	7/8.3%	0.0694	1	0.792
Multimodal action (vortioxetine)	8/18.2%	11/27.5%	19/22.6%	1.04	1	0.308
Others (agomelatine, ademetionine)	11/25.0%	9/22.5%	20/23.8%	0.0722	1	0.788

Similarly, participants were asked to rank all available in the Russian Federation SSRIs by cardiotoxicity (Tables 11 and 12). As a result, there were also no statistically significant differences between the two groups. The safest drugs were sertraline (48.8%), fluoxetine (30.95%) and escitalopram (29.76%). The most cardiotoxic SSRIs were escitalopram (30.95%), paroxetine (29.76%) and citalopram (26.19%). Thus, contradictory results were demonstrated regarding the cardiotoxicity of escitalopram in both study groups: 29.6% - considered it safe, and 30.95% - considered it dangerous. This may be due to the low awareness of doctors about the international FDA recommendations on the high risk of long QT syndrome and the TdP when taking escitalopram [7, 8].

Table 10. Hazard conjugation table for different groups of antidepressants (Kruskal-Wallis test)

Which groups of antidepressants, in your opinion, are the most DANGEROUS in terms of cardiotoxicity?	Specialty		Total participants, N/%	χ^2	df (degrees of freedom)	p-value
	Other specialty, n/%	Neurology, n/%				
TCAs (amitriptyline, clomipramine, imipramine, pipofezine)	35/79.5%	33/82.5%	68/81.0%	0,11720	1	0.732
SSRIs (paroxetine, sertraline, citalopram, escitalopram, fluvoxamine, fluoxetine)	7/15.9%	7/17.5%	14/16.7%	0.0382	1	0.845
SNRIs (milnacipran, duloxetine, venlafaxine)	2/4.5%	2/5.0%	4/4.8%	0.00955	1	0.922
NRI (atomoxetine)	0	2/5.0%	2/2.4%	2.25	1	0.133
Serotonin and alpha-2-adrenergic receptor antagonists (mianserin, mirtazapine)	8/18.2%	11/27.5%	19/22.6%	1.04	1	0.308
Serotonin receptor antagonists and agonists (trazodone)	2/4.5%	4/10.0%	6/7.1%	0.940	1	0.332
Multimodal action (vortioxetine)	2/4.5%	1/2.5%	3/3.6%	0.255	1	0.614
Others (agomelatine, ademetionine)	3/6.8%	0	3/3.6%	2.83	1	0.093

Table 11. Safety contingency table of different SSRIs (Kruskal-Wallis test)

Which SSRI do you think is the SAFEEST?	Specialty		Total participants, N/%	χ^2	df (degrees of freedom)	p-value
	Other specialty, n/%	Neurology, n/%				
Sertraline	24/54.5%	17/42.5%	41/48.8%	1.22	1	0.270
Paroxetine	10/22.7%	8/20.0%	18/21.4%	0.0926	1	0.761
Citalopram	0	3/7.5%	3/3.6%	3.42	1	0.064
Fluoxetine	13/29.5%	13/32.5%	26/31.0%	0.0856	1	0,770
Fluvoxamine	8/18.2%	5/12.5%	13/15.5%	0.517	1	0.472
Escitalopram	11/25.0%	14/35.0	25/29.8%	1.00	1	0.317

Table 12. Hazard conjugation table of various SSRIs (Kruskal-Wallis test)

Which SSRI do you think is the most DANGEROUS?	Specialty		Total participants, N/%	χ^2	df (degrees of freedom)	p-value
	Other specialty, n/%	Neurology, n/%				
Sertraline	4/9.1%	5/12.5%	9/10.7%	0.255	1	0.614
Paroxetine	15/34.1%	10/25.0%	25/29.8%	0.828	1	0.363
Citalopram	13/29.5%	9/22.5%	22/26.2%	0.538	1	0.463
Fluoxetine	6/13.6%	8/20.0%	14/16.7%	0.611	1	0.434
Fluvoxamine	613.6%	5/12.5%	11/13.1%	0.0238	1	0.877
Escitalopram	12/27.3%	14/35.0%	26/31.0%	0.585	1	0.444

Table 13. Cardiotoxic adverse drug reaction

What do you prescribe to prevent antidepressant-cardiotoxic reactions?	Specialty		Total participants, N/%	p-value
	Other specialty, n/%	Neurology, n/%		
Dynamic ECG	13/29.5%	14/35.0%	27/32.1%	0.595
Drug with a low risk of developing an adverse drug reaction	19/43.2%	16/40.0%	35/41.7%	0.814
Consider family history data (sudden death syndrome, prolongation of the QT interval)	12/27.3%	10/25.0%	22/26.2%	0.769
Total	44/100%	40/100%	84/100%	

Assessment of the level of knowledge about the prevention of SSRI-induced prolongation of the QT interval did not show significant differences in the groups of study participants (Table 13). The prevention methods also did not show a statistically significant difference in the groups. Both neurologists and doctors of other specialties in their clinical practice more often use the following methods of prevention of long QT syndrome (p-value > 0.05): ECG in dynamics (32.14%); prescribing antidepressants with a low risk of developing this ADRs (41.67%); study of hereditary history data on cases of long QT syndrome and sudden cardiac death (26.19%).

Most likely, the choice of prescribing antidepressants with a low risk of ADRs as a method of preventing the development of cardiotoxicity is associated with the time limit for collecting complaints, anamnesis, diagnosis and counseling of the patient in outpatient clinical practice. Of great interest are the answers to the question about the clinical observation of cases of long QT syndrome (Table 14). So, 100% of neurologists noted that this ADRs is observed less than once a year, while 13.64% of physicians of other specialties noted that they record this syndrome at least once a year, which is a statistically significant difference between the studied groups specialists (p-value = 0.016).

Table 14. Conjugation tables of the frequency of occurrence of drug-induced prolongation of the QT interval in personal clinical practice

Have you encountered drug-induced prolongation of the QT interval in your practice?	Specialty		Total participants, N/%
	Other specialty, n/%	Neurology, n/%	
1-2 cases per year	4/9%	0	4/4.8%
3 or more times a year	2/4.5%	0	2/2.4%
Rarely	38/86.4%	40/100%	78/92.9%
Total	44/100%	40/100%	84

Table 15. Conjugation tables of QT interval increase during therapy

What increase in the QT interval during therapy makes it possible to diagnose drug-induced long QT syndrome?	Specialty		Total participants, N/%
	Other specialty, n/%	Neurology, n/%	
< 10 msec	6/13.6%	12/30.0%	18/21.4%
10 msec	12/27.3%	12/30.0%	24/28.6%
30 msec	15/34.1%	10/25.0%	25/29.8%
50 msec	11/25.0%	6/15.0%	17/20.2%
Total	44/100%	40/100%	84/100%

Table 16. One-way analysis of variance conjugation tables of long QT interval during therapy

	Meaning	df (degrees of freedom)	p
χ^2	4.29	3	0.232
N	84		

Also, the opinion of experts was analyzed, which increase of delta QT marks the long QT syndrome (Table 15 and 16). No statistically significant differences were found between participants in both groups, but it is alarming that 20.24% of all respondents noted that long QT syndrome should only be identified if the QT interval increases by 50 msec or more.

Opinions on the optimal time for dynamic ECG monitoring while taking antidepressants were examined (Table 17). The majority of participants (57.14%) believe that the optimal time for dynamic ECG monitoring while taking SSRIs is 1 month after the start of antidepressant treatment (without statistically significant difference between groups, p-value > 0.05). It is also alarming that 25% of all participants believe that dynamic ECG should be prescribed 3 months or more after the start of SSRI treatment.

In conclusion, the respondents were asked to answer the question of which cardiotoxic drug effects are provoked by drug-induced prolongation of the QT interval (Figure 3). It was possible to choose several answer options from the following (Table 18).

Table 17. Conjugation table of the optimal time for conducting an ECG in dynamics against the background of taking SSRIs

What is the optimal time to perform a dynamic ECG while taking SSRIs?	Specialty		
	Other specialty, n/%	Neurology, n/%	Total participants, N/%
1 week	10/22.7%	5/12.5%	15/17.9%
1 month	25/56.8%	23/57.5%	48/57.1%
3 months	6/13.6%	8/20.0%	14/16.7%
6 months	3/6.8%	3/7.5%	6/7.1%
12 months	0	1/2.5%	1/1.2%
Total	44/100%	40/100%	84/100%

Table 18. Conjugation tables for manifestations of SSRI-induced QT prolongation

What cardiotoxic events are associated with SSRI-induced prolongation of the QT interval?	Specialty		Total participants, N/%	χ^2	df (degrees of freedom)	p-value
	Other specialty, n/%	Neurology, n/%				
Fainting	13/29.5%	18/45.0%	31/36.9%	2.15	1	0.143
Torsade de pointes	36/81.8%	21/52.5%	57/67.9%	8.26	1	0.004
Chronic fatigue	0	6/15.0%	6/7.1%	7.11	1	0.008
Sudden cardiac death	34/77.3%	24/60.0%	58/69.0%	2.92	1	0.087
Sleep disturbance	1/2.3%	2/5.0%	3/5.0%	0.453	1	0.501

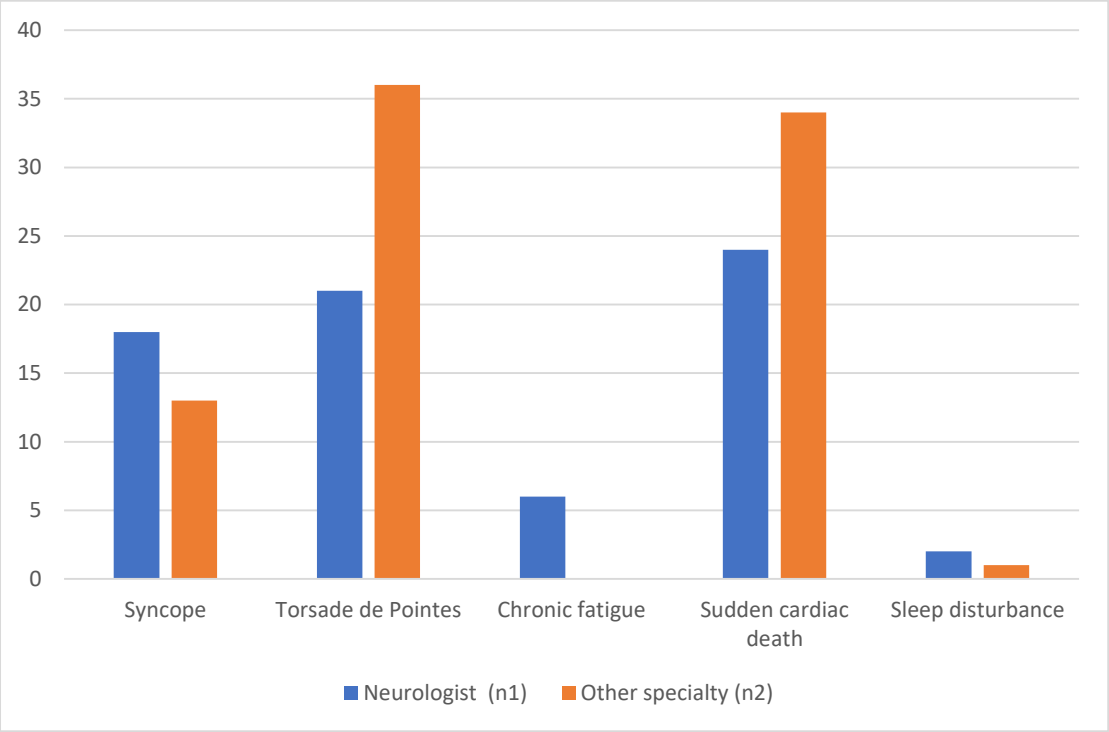

Figure 3. Answer options to the question "*What cardiotoxic events are associated with SSRI-induced prolongation of the QT interval?*"

The most ADRs were: sudden cardiac death (69%), TdP (67.85%), and syncope (36.9%). Statistically significant differences were found between neurologists and other physicians in choosing the following options: TdP (this option was more often chosen by doctors of other specialties, p-value = 0.004); chronic fatigue syndrome (this option was chosen more often exclusively by neurologists, p-value = 0.008).

4. DISCUSSION

Antidepressant-induced cardiotoxic ADRs may occur with varying degrees of probability, which depends on the drug, its dose, and duration of administration. SSRIs may have a heterogeneous effect on the processes of ventricular myocardial repolarization and depolarization, including shortening of the QT interval, lack of effect, borderline prolongation of the QT interval, prolongation of the QT interval. However, due to the high risk of torsadogenicity and sudden death syndrome in patients with long QT syndrome, before prescribing an SSRI, it is important for the attending physician to pay special attention to the identification of modifiable and non-modifiable risk factors for the ADR individually. In the context of limited time allocated per patient in an outpatient clinic, this is quite difficult to achieve, but the results of this systematic review can be used by selecting SSRIs with the lowest risk of QT-related complications in questionable (unspecified) clinical cases, or very cautiously increasing the dose of SSRIs with an average risk of QT-related complications. It is important to perform dynamic ECG at intervals of 1, 3 and 6 months from the start of SSRI administration depending on the risk group (low, medium or high) with QTc calculation using the formula depending on the heart rate, as well as pharmacogenetic testing to exclude the "poor metabolizer" profile, since such patients require drug

monitoring of peak and residual concentrations of the SSRI taken in the blood (peak-trough strategy), especially during long-term treatment with an aggravated family and/or pharmacological history. Undoubtedly, it is important to study the hereditary history (cases of long QT syndrome, TdP and sudden cardiac death syndrome in the pedigree) and, if indicated, conduct targeted DNA sequencing. In general, the presented review emphasizes the relevance of the long QT syndrome problem in clinical practice, which requires an interdisciplinary approach involving neurologists, cardiologists, clinical pharmacologists, and geneticists. Until now, in the world as a whole, and in Russia, in particular, there are no unified approaches to predicting the risks, prevention, and correction of the long QT syndrome. In addition, personalized algorithms and decision-making systems for a practicing physician (neurologist, psychiatrist, clinical pharmacologist) have not been developed. This would facilitate the transfer of the results of fundamental (preclinical) and clinical studies of long QT syndrome into real clinical practice, as well as the introduction of the requirements of current regulatory documents at the level of healthcare institutions.

The presented sociological study demonstrated that doctors are poorly aware of the diagnostic criteria for this adverse reaction and rarely (especially neurologists) identify and register long QT syndrome. Thus, the risk of sudden cardiac death significantly increases. Having analyzed the obtained results, the following ways of improving the dispensary observation of patients taking antidepressants were formulated: increasing awareness and alertness of practicing physicians about the long QT syndrome; ECG monitoring before and during the course of taking antidepressants (including SSRIs); more thorough collection of family history and life history in patients before prescribing antidepressants. The presence of tachycardia, syncope, or anoxic seizures in a patient taking an antidepressant is grounds for suspicion of TdP, a potentially fatal complication of QT syndrome, and requires immediate discontinuation of the drug, replacement with a less cardiotoxic one, 24-hour Holter ECG monitoring, and pharmacogenetic testing.

5. CONCLUSION

The analysis of a survey of physicians using antidepressants in their clinical practice revealed the following statistically significant differences between neurologists and doctors of other specialties who participated in the study. SSRIs (milnacipran, duloxetine, venlafaxine) are much more often prescribed by neurologists than by physicians of other specialties. Neurologists more often prescribe antidepressants for primary headache (tension headache, bundle headache, migraine) and chronic pain syndrome (dorsopathy, painful form of polyneuropathy). Physicians of other specialties are much more likely to prescribe antidepressants for functional dyspepsia and irritable bowel syndrome; neurologists are much more likely to observe mental ADRs (sleep disorders, anxiety, akathisia, suicidal thoughts, asthenia) than physicians of other specialties. Neurologists are much less likely to note prolongation of the QT interval, tachycardia and arterial hypotension as the most common cardiovascular disorders, but they are more likely to note arterial hypertension and bradycardia than doctors of other specialties. Neurologists more often chose arterial hypotension and hypertension as the most life-threatening conditions caused by taking

antidepressants; all neurologists noted that drug-induced prolongation of the QT interval is observed less than once a year, while 13.64% of physicians of other specialties noted that they observe this ADR at least once a year. Also, physicians of other specialties are much more likely to choose the correct answer, that drug-induced prolongation of the QT interval can cause TdP. Exclusively neurologists have noted that SSRI-induced prolongation of the QT interval causes chronic fatigue syndrome. The study highlights the importance of balancing the benefits of antidepressants and safety for the cardiovascular system, especially in vulnerable populations. Addressing these gaps in knowledge and practice can significantly improve patient safety during psychopharmacotherapy.

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