

Use of Original and Generic Fluvoxamine in Clinical Psychiatric and Neurological Practice for the Treatment of Depression (Physician Survey Results)

S.N. Mosolov^{1, 2}, A.S. Avedisova^{1, 3}, E.S. Nemkova⁴

¹ Federal State Budgetary Institution "V.P. Serbsky National Medical Research Centre for Psychiatry and Narcology" of Ministry of Health of the Russian Federation, Moscow, Russia

² Federal State Budgetary Educational Institution of Continuing Professional Education "Russian Medical Academy for Continuing Professional Education" of the Ministry of Health of the Russian Federation, Moscow, Russia

³ State Budgetary Institution of Public Health of the City of Moscow "Research and Clinical Center for Neuropsychiatry of Moscow Healthcare Department named after Z.P. Solovyov", Moscow, Russia

⁴ Pirogov Russian National Research Medical University (RNRMU), Moscow, Russia

SUMMARY

Rationale. Selective serotonin reuptake inhibitors (SSRIs) are the first-line medicinal medications for outpatient treatment of mild to moderate depressive episodes. The existing differences in the efficacy and safety profiles of original and generic medicinal products largely define the therapeutic tactics, complicating the choice of a particular antidepressant by the specialist. Current data comparing original and generic antidepressants are limited, so additional studies are needed.

Objective. To assess the physicians' therapeutic approach and decision flow of physicians regarding the use of antidepressants, including patterns of prescribing original or generic fluvoxamine in their routine practice.

Materials and Methods. 537 physicians from various regions of the Russian Federation participated in the anonymous survey, including 315 (58.66 %) neurologists and 222 (41.34 %) psychiatrists. The SurveyMonkey® tool was used for data collection. The analysis of the obtained results was primarily carried out using descriptive statistical methods.

Results. Over a quarter of psychiatrists (27.5 %) and about a fifth of neurologists (19.4 %) reported negative experiences with generic medications. The key concerns for prescribing generic fluvoxamine were reduced efficacy (psychiatrists 73.0 %, neurologists 77.5 %) and poor tolerability (psychiatrists 62.6 %, neurologists 67.3%). When choosing a generic fluvoxamine, physicians regardless of specialty, were significantly more likely to prescribe a dose exceeding 100 mg to achieve the required therapeutic effect ($p < 0.0001$). Twice as many physicians (17.1 %) reported the onset of the original fluvoxamine effect as early as the first week of use compared to those using the generic (7.6 %). More than half respondents (55 %) assessed the frequency of known adverse events after taking the original fluvoxamine as very rare, with a multiple increase in the frequency of adverse events observed with the generic form (2.4 times for "very common", 2.2 times for "common").

Conclusion. According to the majority of psychiatrists and neurologists surveyed, a more rapid onset of therapeutic effect and a lower frequency of adverse events are observed when using the original fluvoxamine.

KEYWORDS: depression, diagnostics, neuropsychiatry, antidepressants, selective serotonin reuptake inhibitors, fluvoxamine

CONTACTS: Sergey Nikolayevich Mosolov, profmosolov@mail.ru, ORCID: 0000-0002-5749-3964

Alla Sergeevna Avedisova, alla.avedisova@gmail.com, ORCID: 0000-0002-7940-3712;

Ekaterina Sergeevna Nemkova, Katyanem333@gmail.com, ORCID: 0009-0001-5936-5544

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CONFLICT OF INTEREST: The survey under the ATRIUM (Antidepressant TReatment In Unipolar depression Management) clinical study was supported by the Abbott Laboratories LLC.

Rationale

Various types of pharmacotherapeutic and psychotherapeutic interventions are used in treatment of depression. Over the past few decades, antidepressants have become the main type of medication used for the treatment of this disorder. The efficacy, tolerability, and additional effects of antidepressants vary based on their mechanism of action [1]. Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for mild to moderate depression and have a favorable safety and tolerability profile [2].

The emergence of new antidepressants and the active registration of generics may be an indirect reason for the

increase in the prevalence and detectability of depression in the Eastern European countries [3]. In Russia in 2022, for the first time in the last few years, the bioequivalence studies of generics proportion accounted for 69% of all approved clinical trials and exceeded that of original drug products studies [4]. However, according to a survey by the professional community "Doctors of the Russian Federation", 70% of respondents reported that they preferred original medicines when prescribing treatment [5]. A recent survey of the opinion of physicians visiting the Medscape website showed that substituting an original drug with a generic can affect treatment outcomes [6].

The increase in the number of generics requires closer attention to, and enhanced control of their quality,

efficacy and safety [7]. Physicians are concerned about the use of generics due to their limited efficacy, safety and tolerability data. As per current requirements for marketing authorization of the original drug or reference product, the efficacy, safety profile and side effects must be confirmed in preclinical and several phases of clinical studies [8, 9]. While in order to obtain marketing authorization for a generic drug, conducting a bioequivalence study, that is, confirming the absorption rate, excretion rate and amount of medicinal product reaching the systemic bloodstream in healthy volunteers being the same as with the original drug product, is sufficient. And for a number of key pharmacokinetic parameters, such as AUC (area under curve) and C_{max} (maximum blood plasma concentration of the substance), a certain deviation relative to the original product is allowed. The parameters should fall within the range of 80.0–125.0% [8, 9]. Differences in the efficacy and tolerability profile of generic and original drugs identified via studies may be due to the initial quality of the pharmaceutical substance, differing in excipients and process technology. A literature search of eLIBRARY.RU, Google Scholar, and PubMed databases revealed limited data comparing the original and generic antidepressants.

For the assessment of physicians' opinion on the efficacy and tolerability of original and generic drug products in the treatment of depression, an online survey of psychiatrists and neurologists was conducted.

Survey method

The physicians were surveyed through anonymous questionnaire. The SurveyMonkey® tool was used for data collection. The respondents were asked to answer 28 questions from the study protocol, and the survey did not include fields for personal data (contact information) collection. Each participant could only participate in the survey once and was restricted from completing the questionnaire again by IP address filtering. The study included data only from the respondents who have completed the questionnaire in full. There were two main types of questions: single and multiple choice. We can divide this questionnaire into three sections: respondents socio-demographic characteristics (5 questions), questions regarding specifics of diagnosis and therapy choice for depression (12 questions), assessment of the experience with original and generic fluvoxamine drugs in treatment of patients with depression (15 questions). This paper presents the comparison of the results of the physicians' opinions on the experience with the original and generic antidepressant. Given the substantial amount of data collected, it seems feasible to describe approaches to the diagnosis and treatment of depression in a separate paper.

The analysis of study results was primarily carried out using descriptive statistics methods. Qualitative parameters are presented as the number and percentage of physicians in each category. For the purposes of results simplification, the figures were rounded to tenths. Wilcoxon test was used to compare doses of original and generic fluvoxamine. The paired Student's t-test was used to compare quantitative data. To compare categorical data in independent groups, the chi-square test was used; if the conditions for the chi-square test were not

met, Fisher's exact test was used. McNemar test was used to compare two related (dependent) groups by qualitative variables.

Survey participants

Data were collected anonymously between December 2021 and the end of January 2022. By the end of the study, responses were received from 537 physicians from various regions of the Russian Federation.

Physicians specialized in psychiatry and/or neurology who treat patients with depression of various origins were asked to participate in the survey. Two reminder messages were forwarded to participants during the data collection period. Data from physicians of other specialties were excluded from the study.

A total of 8369 messages were sent to invite physicians to participate in the survey via e-mail (5882 e-mails) and text messages (2487 text messages). Physicians who confirmed their specialty and agreed to provide their email address or telephone number to the sponsor of this study in accordance with current legislation on the retention of personal data were included in the mailing list. The percentage of respondents who had completed the questionnaire ($n = 537$) in relation to the total number of messages (via e-mail and text messages) sent was thus 6.4%.

Of 551 physicians who had visited the questionnaire page, 537 completed it. As a result, when assessing the survey compliance of physicians, the proportion of users who completed the survey vs. those who visited the questionnaire page was found to be 97.5%.

The survey involved physicians from 100 cities of the Russian Federation from all eight federal districts, including 94 (17.5%) physicians from Moscow and 51 (9.5%) physicians from Saint Petersburg.

Results

Of the 537 surveyed physicians, 58.7% (315 physicians) were neurologists, and 41.3% (222 physicians) were psychiatrists. Work experience in respective specialty ranged from 1 to 50 years. The average work experience among the surveyed psychiatrists was 19.2 years (median 20.0; standard deviation 9.9), and 18.3 years (median 18.0; standard deviation 9.9) for neurologists. Among the respondents, 74.9% (402) physicians worked in outpatient clinics (neurologists 78.1% (246), psychiatrists 70.3% (156)), 7.3% (39) in hospitals (neurologists 7.3% (23), psychiatrists 7.2% (16)) and 17.9% (96) combined work in a hospital and outpatient clinic (neurologists 14.6% (46), psychiatrists 22.5% (50)), 57.2% (307) worked in public institutions (neurologists 50.5% (159), psychiatrists 66.7% (148)) and 26.3% (141) in private healthcare institutions (neurologists 34.6% (109), psychiatrists 14.4% (32)). Thus, the survey respondents primarily worked in the outpatient and government institutions.

SSRIs are recommended as first-line therapy for mild to moderate depressive episodes [10]. According to the survey results, out of SSRIs 76.0% (408) of the respondents prescribed fluvoxamine, 64.3% (345) escitalopram and 50.5% (271) sertraline; respondents reported significantly less frequent use of fluoxetine (23.7% (127)) and paroxetine (115 (21.4%)) in clinical practice. This study

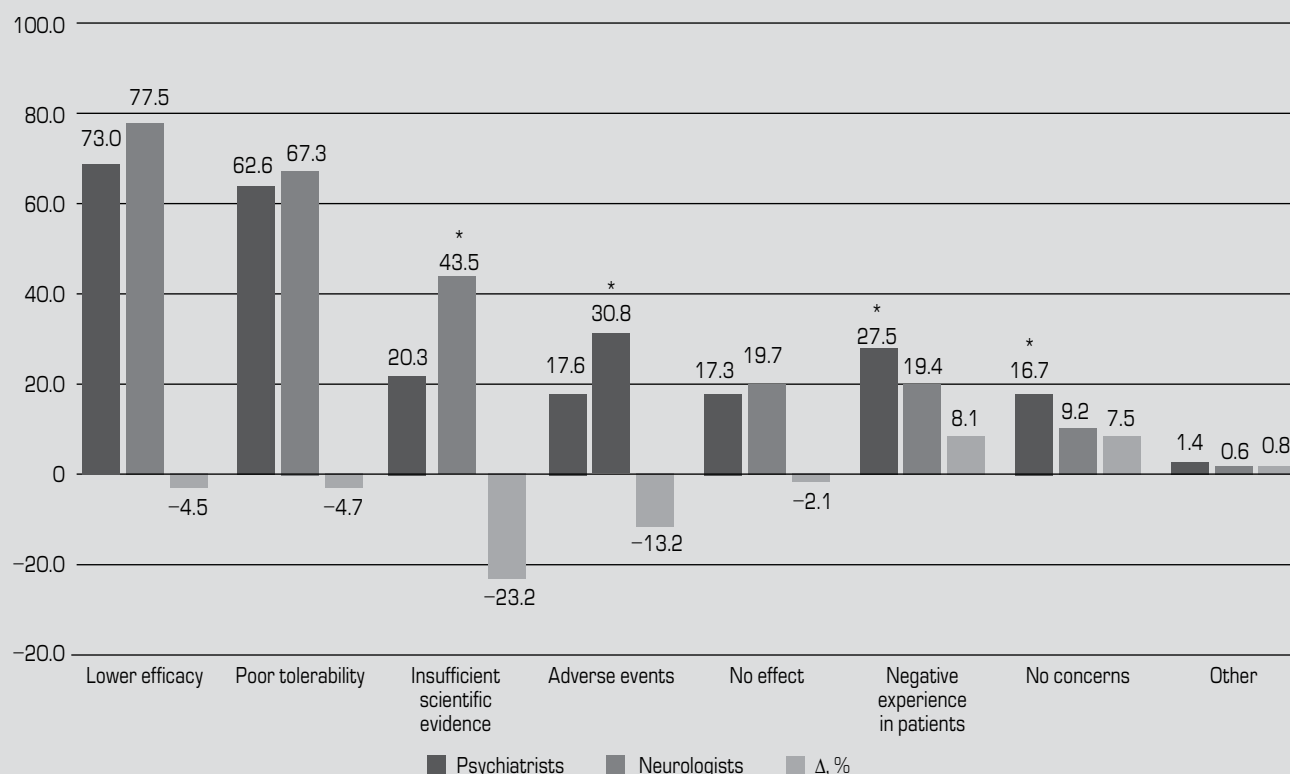


Figure 1. Concerns on prescribing a generic drug, % of physicians' opinions

Note. Δ (delta) = % psychiatrists – % neurologists, * – $p < 0.05$

compared respondents' opinions regarding their experience of prescribing original and generic drugs using fluvoxamine as an example, as one of the widely used antidepressants.

The respondents reported prescription of the original fluvoxamine to a greater number of patients: psychiatrists on average 52.9% (median 50.0%, standard deviation 26.8%), neurologists on average 49.3% (median 50.0%, standard deviation 30.7%), than the generic product: psychiatrists on average 32.8% (median 25.0%, standard deviation 24.1%), neurologists on average 24.4% (median 20.0%, standard deviation 21.6%).

Most respondents (87.7% (471)) reported concerns when choosing between the original and generic medicines in treatment of depression. Both psychiatrists and neurologists gave approximately the same number of answers to the question about concerns regarding the prescription of generics (Fig. 1): possible lower efficacy (psychiatrists 73.0% (162), neurologists 77.5% (244)) and poor tolerability (psychiatrists 62.6% (139), neurologists 67.3% (212)).

More significant differences were observed in the items "insufficient scientific evidence of efficacy and safety" (psychiatrists 20.3% (45), neurologists 43.5% (137)), as well as "safety issues" (psychiatrists 17.6% (39), neurologists 30.8% (97)), where neurologists were twice as concerned. These results may be due to the high prevalence of patients with comorbidity in routine neurological practice. Another possibility is that neurologists are less aware of the efficacy and safety of antidepressants than psychiatrists, which could indirectly explain the increased level of concern.

More than a quarter of psychiatrists (27.5% (61)) and about a fifth of neurologists (19.4% (61)) reported negative experiences with generic drugs. The lack of effect was reported by 18.8% (101) of the respondents, without significant differences between the psychiatrists and neurologists' opinions (Fig. 1). Notably, neurologists express more concerns per majority of items despite the greater negative experiences with generics among psychiatrists.

The effective dose of fluvoxamine, according to most respondents, was 100 mg (Fig. 2). However, fewer respondents reported the efficacy of the 100 mg dose when using a generic drug: 64.4% (346) for the original drug and 58.2% (316) for the generic. Both neurologists and psychiatrists more often reported the need to prescribe higher doses of generic fluvoxamine to achieve a therapeutic effect: the effective dose of 150 mg or more was more often reported by physicians for the generic drug (23.65% vs. 16.2% for the original drug).

Neurologists reported the effective dose of 50 mg twice more often for both the original (psychiatrists 12.6% (28), neurologists 24.1% (76)) and the generic drug (psychiatrists 12.2% (27), neurologists 21.3% (67)). In turn, psychiatrists were twice as likely to report a dose of 150 mg as effective for both the original (psychiatrists 14.9% (33), neurologists 7.3% (23)) and the generic fluvoxamine (psychiatrists 22.5% (50), neurologists 11.1% (35)). Psychiatrists were much more likely to report the use of higher doses (250 mg, 300 mg) when choosing the generic product. Neurologists reported the need to use doses of 250 mg and 300 mg only when prescribing the generic drug.

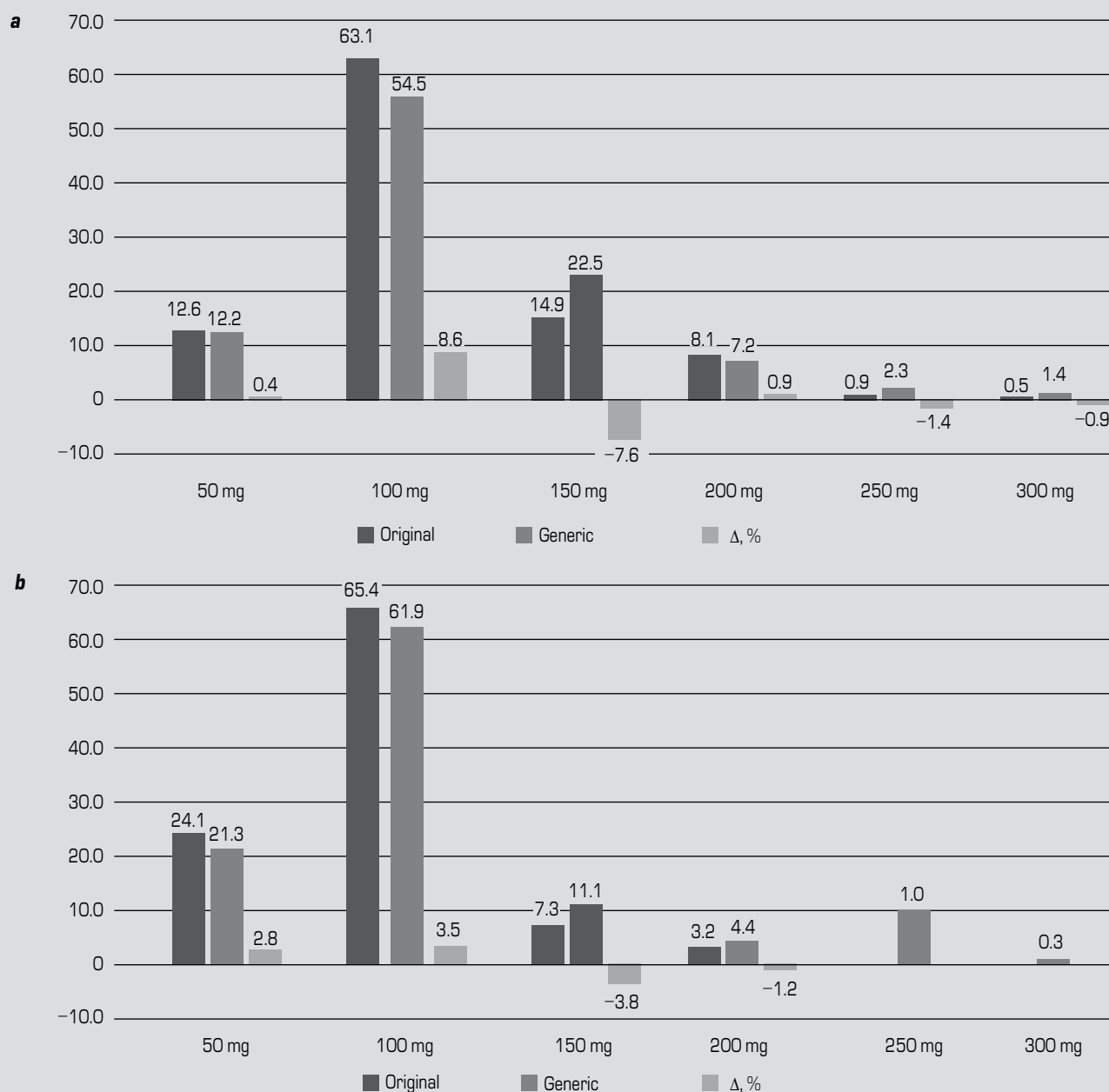


Figure 2. Effective doses comparison of original and generic fluvoxamine: **a** – psychiatrists opinions, %; **b** – neurologists opinions, %

Note: Δ (delta) = % original – % generic, * – $p < 0.05$

When comparing the effective doses of the original and generic fluvoxamine, a noticeable shift towards neurologists prescribing higher doses of fluvoxamine when choosing a generic drug (doses of 150, 250, 300 mg) can be observed. In the case of the original drug, neurologists more often used the doses of 50 and 100 mg compared to the generic drug, suggesting that neurologists are more doubtful of the generic drug, reflecting their concerns described above (Fig. 1). The effective doses of the generic fluvoxamine were significantly higher than those of the original drug ($p < 0.05$). Additional statistical analysis revealed that when choosing a generic drug, physicians, regardless of specialty, were significantly more likely to prescribe a dose exceeding 100 mg to achieve the required therapeutic effect ($p < 0.0001$).

Moreover, most respondents of both specialties reported the therapeutic effect of both original and generic fluvoxamine being most often observed after 2 weeks of use (Fig. 3).

According to the physicians, the onset of the therapeutic effect occurred faster when using the original vs. the generic fluvoxamine. 17.1% (92) of physicians of both specialties when choosing the original drug product, reported therapeutic effect in just 1 week, which is twice as often as when choosing the generic (7.6% (41)) (Fig. 3). When analyzing the combined responses regarding the onset of therapeutic effect by the end of 1 and 2 weeks, it was shown that 64.4% (326) of physicians noted the onset of therapeutic effect by the end of 1 or 2 weeks when using the original fluvoxamine, and 44.7% (240) of physicians noted the effect when using the generic.

Additionally, fluvoxamine-associated adverse events were assessed. Most respondents rated the frequency of known adverse events after taking the original fluvoxamine as very rare (55% on average). 79% of the respondents reported the frequency of vomiting as very rare, while 10% reported the frequency of nausea as common. When assessing the tolerability of therapy with a generic fluvoxamine, respondents of both specialties reported the risk of developing adverse events multiple times more often. "Average frequency of adverse events" was introduced as a comparative analysis parameter. According to physicians, the use of generic fluvoxamine is associated with a greater risk of developing adverse events compared to the original drug: a 2.4-fold increase in the frequency of "very common" adverse events and a 2.2-fold increase of "common" adverse events was observed. It should be noted that all of the listed adverse events are mentioned in the Patient Information Leaflet for fluvoxamine, thus they are neither new nor unknown [11].

According to the respondents of both specialties, when using the original fluvoxamine, the need for dose reduction was most often caused by the occurrence of such adverse events as dyspepsia, tremor, increased sweating, vomiting and nausea. Sexual dysfunction and muscle cramps had the least impact on the decision to reduce the dose of antidepressant. Similar responses to the question about the reasons for dose reduction when using generic fluvoxamine were obtained.

By pooling the data on the original and generic fluvoxamine and comparing the opinions of psychiatrists and neurologists, it was found that neurologists more often reported symptoms such as dyspepsia, body weight fluctuations and vomiting as the reasons for dose reduction. Respondents from the neurologist subgroup reported a greater number of significant reasons for reducing the drug dose, suggesting greater concern about adverse events which develop from the use of antidepressants (see Fig. 1).

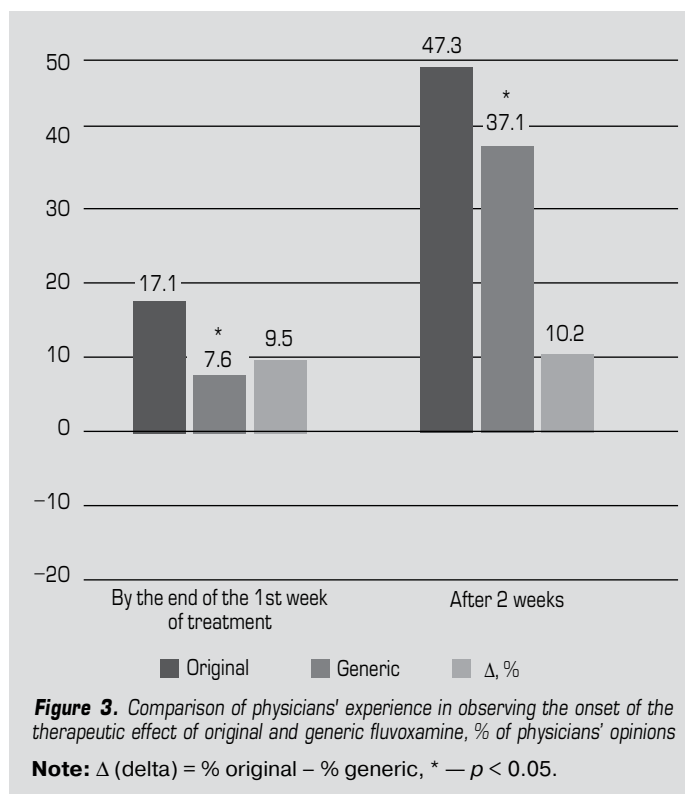
According to psychiatrists and neurologists, adverse events following the administration of the original fluvoxamine occurred less frequently and were less likely to lead to discontinuation, with dose reduction being sufficient. However, following the administration of the generic product, treatment adjustment by changing the dose was less often possible, and discontinuation or switching to another antidepressant was required more frequently.

Discussion

Survey results indicate the need to carry out full-fledged comparative pharmacokinetic and clinical studies of drugs equivalence to establish the reasons for the differences in the clinical effect and tolerability between the original and generic fluvoxamine.

According to the results of the survey, the average effective dose of the original and reproduced fluvoxamine was 100 mg. The effective dose of fluvoxamine was higher for the generic compared to the original drug.

A trend was identified for neurologists to prescribe lower doses of antidepressants, which may be both attributed to the neurologists concerns over prescribing higher doses in connection with the increased risk of adverse events, and the need for psychiatrists to use



higher doses of the drug due to the management of more difficult-to-cure patients with drug-resistant mental disorders. Neurologists did not use the original fluvoxamine in doses above 200 mg/day, but used the generic drug in high doses (250 mg, 300 mg), suggesting neurologists being uncertain of the sufficient efficacy of the generic form.

According to all respondents, the most pronounced therapeutic effect of fluvoxamine occurred after 2 weeks of taking either the original or the generic drug. However, when the original drug was prescribed compared to the generic product, in some patients it occurred faster: after 1 week, and the effect of the generic drug compared to the original product was slower: after 3-4 weeks of therapy.

The primary physicians' concerns, regardless of the specialty, associated with the use of a generic drug were its possible lower efficacy and poor tolerability. Compared to psychiatrists, neurologists were twice as likely to doubt the sufficiency of scientific evidence of the efficacy and safety of generic drugs, and psychiatrists were more likely than neurologists to avoid prescribing a generic drug due to the negative experience of patients, which is directly related to the higher frequency of prescribing antidepressants among psychiatrists.

More than half of the respondents rated the frequency of known adverse events after taking the original fluvoxamine as very rare (vomiting and muscle cramps were especially rare). Most psychiatrists and neurologists reported a manifold increase in the frequency of adverse events when using the generic fluvoxamine compared to the original medication. These symptoms included nausea, dyspepsia, vomiting, tremors, body weight fluctuations, sexual dysfunction, increased sweating and muscle cramps.

According to the physicians of both specialties, the need for original and generic fluvoxamine dose reduction was most often caused by symptoms ranked by frequency: nausea, increased sweating, tremor, dyspepsia, and vomiting. Sexual dysfunction had less impact on dose reduction due to lower frequency.

According to all respondents, adverse events following administration of the original fluvoxamine occurred less frequently and were less likely to lead to discontinuation, with dose reduction often being sufficient. At the same time, it was less often possible to adjust the dosage of the reproduced drug to correct the treatment, and treatment discontinuation or switching to a different antidepressant was more often required. The most common adverse events leading to discontinuation of the original or generic drug and switching to another antidepressant were vomiting, muscle cramps, and sexual dysfunction.

In conclusion, the study limitations must be noted. To start with, no statistical assessment of this study population representativeness was performed. However, a comparison of the study population with the population of neurologists and psychiatrists based on data obtained from publicly available sources showed that they have similar characteristics in terms of the ratio of the number of neurologists and psychiatrists (315 neurologists and 222 psychiatrists compared to 28.9 thousand neurologists and 22.1 thousand psychiatrists in the general population), the distribution of physicians by federal districts of the Russian Federation, with a predominance of the Central Federal District (about 30% of the physicians

participating in the study and about 30% of neurologists and psychiatrists in the general population belonged to the Central Federal District) [12]. Also, when assessing the efficacy and tolerability parameters of fluvoxamine (average time of effect onset, frequency of adverse events, reasons for dose reduction and discontinuation), it is recommended to compare the results with the used dose of the drug.

Conclusion

Despite their experience with generic drugs, the vast majority of physicians surveyed expressed concerns about their possible lower efficacy and tolerability. This survey compares the opinions of psychiatrists and neurologists on the use of original and generic drugs in the treatment of depression using fluvoxamine as an example. When using the original fluvoxamine, compared to the generic drug, a more rapid therapeutic effect onset and a lower frequency of adverse events were observed. As per the survey results, the effective dose of fluvoxamine was higher for the generic drug compared to the original, while the therapeutic effect onset, according to physicians, occurred faster when using the original fluvoxamine than the generic drug.

The results of the study confirm the need for additional studies on the use of original and generic drug products in the treatment of depression to obtain reliable data which may influence the decision-making process for selecting treatment strategies in routine clinical practice.

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