This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of MID-NET® study: No. 2020-002

January 10, 2024

Study title

Evaluation of the effect of antidepressants on indices of decreased platelet count using MID-NET®

Products investigated

Selective serotonin reuptake inhibitors (hereinafter referred to as “SSRIs”) shown below:

- Escitalopram oxalate
- Sertraline hydrochloride
- Paroxetine hydrochloride hydrate
- Fluvoxamine maleate

Serotonin and noradrenaline reuptake inhibitors (hereinafter referred to as “SNRIs”) shown below:

- Duloxetine hydrochloride
- Venlafaxine hydrochloride
- Milnacipran hydrochloride

Serotonin reuptake inhibitor/serotonin receptor modulator shown below

- Vortioxetine hydrobromide

Background:

Regarding SSRIs, SNRIs, and vortioxetine hydrobromide, which are antidepressants, a precaution for decreased platelet count is included in the Clinically Significant Adverse Reactions section in the Information on PRECAUTIONS, etc., or in the Other Adverse Reactions section for some of the drugs, while no precaution is included in either section for some of the drugs. Thus, the status of issuance of precautions differs among the drugs (Table 1).

Table 1. Descriptions on decreased platelet count in Information on PRECAUTIONS, etc. of the drugs investigated

Category	Non-proprietary name	Descriptions on decreased platelet count	
		Clinically Significant Adverse Reactions	Other Adverse Reactions
SSRIs	Escitalopram oxalate	Not described	Described
	Sertraline hydrochloride	Not described	Described
	Paroxetine hydrochloride hydrate	Described	Not described
	Fluvoxamine maleate	Described	Not described
SNRIs	Duloxetine hydrochloride	Not described	Not described
	Venlafaxine hydrochloride	Described	Not described
	Milnacipran hydrochloride	Not described	Not described
Serotonin reuptake inhibitor/ serotonin receptor modulator	Vortioxetine hydrobromide	Not described	Not described

- Although it would be valuable to evaluate the risk of decreased platelet count and determine the necessity of issuing new or additional precautions for the above drugs, it may be difficult to evaluate the causal relationship between the suspected drug and the adverse drug reaction based on individual case reports for each drug due to the effects of other drugs, underlying diseases, etc. in some cases. In addition, no preceding studies that quantitatively evaluated the risk of decreased platelet count among the drugs have been reported.
- In this study, the risk of decreased platelet count after prescriptions of SSRIs, SNRIs, and vortioxetine hydrobromide in patients with depression was examined.

Purpose of the study

To evaluate the risk of decreased platelet count for SSRIs, SNRIs, and vortioxetine hydrobromide by calculating incidences of decreased platelet count after prescriptions of each preparation in patients with depression, in comparison to that for paroxetine hydrochloride hydrate

Reason to select MID-NET® for the study and data period

Reason to select: To perform evaluation with laboratory test results as an index

Data period: January 1, 2009 to March 31, 2021
Data from all healthcare organizations cooperating with MID-NET® (22 hospitals at 10 healthcare organizations) whose data were available throughout the target data period

Outline of method

- **Study Design**

  Cohort design

- **Study population**

  Patients who were newly prescribed any of the SSRIs, SNRIs, and vortioxetine hydrobromide during the data period and had a diagnosis of depression in the same month as the day of a new prescription were identified. A new prescription was defined as a case where a medical record more than 180 days before the first prescription during the data period was available (where it was confirmed that neither SSRIs, SNRIs, nor vortioxetine hydrobromide had been prescribed within 180 days prior to the first prescription date). Of the identified patients, the following were excluded: a) Patients who received an antidepressant other than the drugs investigated 1 to 180 days prior to the day of a new prescription, b) patients who had a laboratory test result of platelet count less than 100 000/mm^3 1 to 180 days prior to the day of a new prescription, c) patients who had a diagnosis of thrombocytopenia 1 to 180 days prior to the day of a new prescription, d) patients who had a diagnosis of cancer or received antineoplastic agent(s) 1 to 180 days prior to the day of a new prescription, e) patients who were prescribed more than 1 antidepressant on the day of a new prescription. Patients who did not meet these exclusion criteria were included in the study population.

  This study included 9 exposure groups (1) escitalopram group, 2) sertraline group, 3) fluvoxamine group, 4) duloxetine group, 5) venlafaxine group, 6) milnacipran group, 7) vortioxetine group, 8) SSRIs group (an integrated group of group 1) to 3)), and 9) SNRIs group (an integrated group of group 4) to 6))) as well as a comparator group (paroxetine group), in accordance with the active ingredient of the drug prescribed at the day of a new prescription. Paroxetine hydrochloride hydrate was used as a positive control since a precaution for decreased platelet count is specified in the Clinically Significant Adverse

Reactions section in the Information on PRECAUTIONS, etc.

- **Outcomes**

  Decreased platelet count was defined as a platelet count less than 100 000/mm^3 (equivalent to grade 1 or higher by "Criteria of Severity of Adverse Drug Reactions for Drugs, etc." (PAB/SD Notification No. 80 issued by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992 (hereinafter referred to as the "Severity Criteria")).

- **Follow-up period** A follow-up period, during which the occurrence of outcomes was identified, started at the day of a new prescription and ended at the earliest day of the following: a) The date of the occurrence of outcomes, b) the date of completion of a prescription continuation period*1, c) the date of a prescription of an antidepressant other than the one prescribed on the day of a new prescription, or d) the date of the final medical record.

  *1 A prescription continuation period was defined as a period during which prescriptions were considered to be continuous in cases where the period between the end date of the preceding prescription period and the start date of the following prescription period was less than or equal to 30 days (hereinafter referred to as "gap period"). The end date of the prescription continuation period was defined as the date when the last prescription period plus 30 days (hereinafter referred to as "grace period") had passed since the start date of the last prescription.

- **Analyses and methods**

  [Primary analysis]

  For the 9 exposure groups, crude hazard ratios and adjusted hazard ratios weighted by the inverse of the propensity score in comparison to the paroxetine group were estimated using the Cox proportional hazards model. Of note, propensity scores were estimated using a logistic regression model for each combination of the exposure group and comparator group.

  [Secondary analysis]

  The same analysis as the primary analysis was performed for a patient population including patients without a diagnosis of depression in the same month as the day of a new prescription.

  [Sensitivity analysis]

  To confirm the robustness of the primary analysis, adjusted hazard ratios were estimated for the primary analysis when the conditions were changed as described below:

  - Sensitivity analysis 1: The outcome definition was changed to a platelet count less

than 100 000/mm^3 or a diagnosis of thrombocytopenia.

- Sensitivity analysis 2: The outcome definition was changed to a platelet count less than 75 000/mm^3 (equivalent to grade 2 or higher*2 by Common Terminology Criteria for Adverse Events Version 5.0 (hereinafter referred to as “CTCAE”)).

  *2 Equivalent to grade 2 or higher by the Severity Criteria
- Sensitivity analysis 3: The outcome definition was changed to a platelet count less than 50 000/mm^3 (equivalent to grade 3 or higher*3 by CTCAE)).

  *3 Equivalent to grade 3 by the Severity Criteria
- Sensitivity analysis 4: The gap period and grace period were changed to 90 days.
- Sensitivity analysis 5: "The date when 14 days had passed since the start of a follow-up period" was added to the conditions for determining the end date of a follow-up period.

Outline of results

■ Study population

- A total of 18 530 patients were identified who were newly prescribed SSRIs, SNRIs, or vortioxetine hydrobromide during the data period and had a diagnosis of depression in the same month as the day of a new prescription, with 10 407 patients out of them not meeting the exclusion criteria.
- The number of patients in each group and distribution of patients’ age and sex are shown in Table 2.

Table 2. Number of patients and distribution of patients' age and sex

	Number of patients	Age	Sex
		Median (interquartile range)	Number of male patients (%)*
Paroxetine group	2 196	62.0 (43.0−75.0)	728 (33.2)
Escitalopram group	1 434	46.0 (32.0−66.0)	471 (32.8)
Sertraline group	2 113	51.0 (35.0−71.0)	630 (29.8)
Fluvoxamine group	1 212	50.0 (31.0−71.0)	402 (33.2)
Duloxetine group	2 934	63.0 (46.0−75.0)	1 165 (39.7)
Venlafaxine group	139	50.0 (38.0−65.0)	48 (34.5)
Milnacipran group	367	61.0 (44.0−74.0)	115 (31.3)
Vortioxetine group	12	42.5 (25.0−59.0)	< 10 (< 83.4)
SSRIs group	4 759	49.0 (33.0−70.0)	1 503 (31.6)
SNRIs group	3 440	62.0 (46.0−74.0)	1 328 (38.6)

* Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

- Even after weighting by the inverse of the propensity score, imbalances in patient background factors (adjustment factors used for estimating propensity scores) with an absolute standardized difference greater than 0.1 compared to the paroxetine group were observed for the venlafaxine group and vortioxetine group among the 9 exposure groups.

■ **Risk of decreased platelet count**

- The results of the primary analysis are shown in Table 3. Hazard ratios could not be estimated for the vortioxetine group since no occurrence of outcomes was observed. For the other groups, no significant increase in risk compared to the paroxetine group was observed. Among escitalopram, sertraline, duloxetine, milnacipran, and vortioxetine, for which no precaution for decreased platelet count is included in the Clinically Significant Adverse Reactions section in the Information on PRECAUTIONS, etc., the point estimate of the adjusted hazard ratio was higher than 1 for the sertraline group only.

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Table 3. Results on risk of decreased platelet count (primary analysis)

	Number of patients	Follow-up period (person-year)	Number of outcome occurrences*	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Paroxetine group	2 196	1183.8	39	reference	reference
Escitalopram group	1 434	698.4	< 10	0.45 (0.19−1.11)	0.53 (0.21−1.33)
Sertraline group	2 113	1189.7	37	1.31 (0.83−2.06)	1.23 (0.78−1.94)
Fluvoxamine group	1 212	761.4	22	1.46 (0.83−2.56)	1.48 (0.87−2.51)
Duloxetine group	2 934	1 529.8	32	0.73 (0.44−1.23)	0.74 (0.45−1.20)
Venlafaxine group	139	48.5	< 10	0.77 (0.06−9.17)	0.48 (0.07−3.28)
Milnacipran group	367	155.4	< 10	0.83 (0.28−2.39)	0.70 (0.26−1.93)
Vortioxetine group	12	1.3	0	Incalculable	Incalculable
SSRIs group	4 759	2 744.3	66	1.13 (0.75−1.69)	1.14 (0.76−1.70)
SNRIs group	3 440	1 776.3	39	0.78 (0.48−1.26)	0.77 (0.48−1.21)

* Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.
† Weighted by the inverse of the propensity score. The propensity score was estimated by using adjustment factors shown below. Adjustment factors: Sex, age, concomitant drugs (gold preparations, penicillamine, sulfisoxazole, sulfamethoxazole/trimethoprim (ST) combination drugs, quinidine, thiazide diuretics, sodium valproate, carbamazepine, ranitidine, rifampicin, interferon preparations, infliximab, penicillin, amoxicillin, acetaminophen, heparin, proton pump inhibitors, NSAIDs), complications (hepatic impairment, renal impairment, myelosuppression, coagulopathy, infections, autoimmune disease), pregnancy

- As a result of sensitivity analyses for the sertraline group, each sensitivity analysis including sensitivity analysis 3 (adjusted hazard ratio: 1.29 (95% confidence interval (CI) 0.45−3.71)) tended to show a point estimate of the adjusted hazard ratio higher than 1 as the primary analysis did.
- For the milnacipran group, the sensitivity analysis 1, 2, and 4 tended to show point estimates of adjusted hazard ratios lower than 1 in a similar manner to the primary analysis (the adjusted hazard ratio of 0.91 (95% CI 0.36−2.33) for the sensitivity analysis 1, 0.41 (95% CI 0.06−3.02) for the sensitivity analysis 2, and 0.70 (95% CI 0.28−1.73) for the sensitivity analysis 4), while the sensitivity analysis 3 and 5 tended to show point estimates of adjusted hazard ratios above 1 contrary to the primary analysis (the adjusted hazard ratio of 1.21 (95% CI 0.15−9.57) for the sensitivity analysis 3 and 1.11 (95% CI 0.33−3.77) for the sensitivity analysis 5).
- Regarding the groups other than the above, for the fluvoxamine group and SSRIs group, each sensitivity analysis tended to show a point estimate of the adjusted hazard ratio

above 1 in a similar manner to the primary analysis. For the escitalopram group, duloxetine group, venlafaxine group, and SNRIs group, each sensitivity analysis tended to show a point estimate of the adjusted hazard ratio below 1 in a similar manner to the primary analysis.

- The results of the secondary analysis are shown in Table 4. For each group, the tendencies were similar to those in the primary analysis.

Table 4. Results on risk of decreased platelet count (secondary analysis)

	Number of patients	Follow-up period (person-year)	Number of outcome occurrences*	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Paroxetine group	3 732	2 083.8	82	reference	reference
Escitalopram group	1 883	844.8	11	0.50 (0.26- 0.97)	0.52 (0.27−1.03)
Sertraline group	3 238	1 823.8	58	1.09 (0.78−1.53)	1.02 (0.72−1.43)
Fluvoxamine group	2 139	1 389.8	39	1.18 (0.79−1.75)	1.17 (0.79−1.73)
Duloxetine group	9 671	4 894.7	96	0.48 (0.35−0.66)	0.49 (0.35−0.67)
Venlafaxine group	201	60.6	< 10	1.26 (0.30−5.22)	0.46 (0.12−1.80)
Milnacipran group	568	306.5	< 10	0.87 (0.43−1.75)	0.73 (0.37−1.44)
Vortioxetine group	16	1.4	0	Incalculable	Incalculable
SSRIs group	7 260	4 206.3	110	0.99 (0.74−1.32)	0.98 (0.73−1.32)
SNRIs group	10 440	5 325.8	109	0.51 (0.38– 0.70)	0.51 (0.38−0.70)

* Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.
† Weighted by the inverse of the propensity score. The propensity score was estimated by using adjustment factors shown below. Adjustment factors: Sex, age, concomitant drugs (gold preparations, penicillamine, sulfisoxazole, ST combination drugs, quinidine, thiazide diuretics, sodium valproate, carbamazepine, ranitidine, rifampicin, interferon preparations, infliximab, penicillin, amoxicillin, acetaminophen, heparin, proton pump inhibitors, NSAIDs), complications (hepatic impairment, renal impairment, myelosuppression, coagulopathy, infections, autoimmune disease), pregnancy

■ Discussion based on the results

- Considering that primary analysis and each sensitivity analysis including the sensitivity analysis 3 tended to show point estimates of adjusted hazard ratios above 1 for the sertraline group, it was suggested that the risk of decreased platelet count for sertraline hydrochloride is possibly comparable to that for paroxetine hydrochloride hydrate, irrespective of the severity of decreased platelet count.
- Precautions for decreased platelet count are not included in the Clinically Significant Adverse Reactions section in the Information on PRECAUTIONS, etc. except for

fluvoxamine maleate and venlafaxine hydrochloride. However, since point estimates of adjusted hazard ratios tended to be lower than 1 for all the groups excluding sertraline hydrochloride (no occurrence of outcomes in the vortioxetine group), the results of this study do not suggest that these drugs have a risk of decreased platelet count comparable to that for paroxetine hydrochloride hydrate.

- It should be noted that there are some limitations, such as the possibility that other potential confounders (e.g., performance status of patients, severity of depression, detailed treatment history) may have affected the results. In addition, it should also be noted that the point estimate for each exposure group shown in this study does not necessarily indicate the magnitude of correlations of the risk of decreased platelet count for each exposure group. This is because propensity scores were estimated for each combination of an exposure group and a comparator group, and comparability among exposure groups was not ensured.

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp