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Comparative effects of 15 antidepressants on the risk of Withdrawal Syndrome: A real-world study using the WHO pharmacovigilance database

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1 Introduction

2 Several case reports, supported by numerous quantitative studies, have highlighted
3 withdrawal syndromes after antidepressants discontinuation, with physical and psychiatric
4 symptoms appearing after drug discontinuation or decrease.^{1, 2, 3, 4, 5, 6, 7} A systematic review
5 mentions that it would concern on average 56% of the patients treated, with 46% experiencing
6 “severe” symptoms.⁸ Some clinical trials have suggested that short half-life antidepressants may
7 have a higher risk of withdrawal syndromes than long half-life antidepressants.^{9, 10, 11} However,
8 these clinical trials had several limitations including outcome misclassification, a very limited
9 panel of antidepressants, lack of power.^{12, 13} Moreover, most studies did not use appropriate
10 methods to collect symptoms and distinguish withdrawal syndromes from rebounds and
11 recurrence. Recent systematic reviews also mentioned a lack of epidemiological and socio-
12 demographic data, which could in part be provided by pharmacovigilance databases.¹⁴ There is
13 therefore a need to further evaluate the risk of withdrawal syndrome in patients taking
14 antidepressants in a large-scale study including the most common antidepressants under
15 everyday life conditions. Here, we compared the risk of reporting withdrawal syndrome between
16 15 antidepressants (Selective Serotonin Reuptake Inhibitors [SSRIs], Serotonin and
17 Norepinephrine Reuptake inhibitors [SNRIs], and atypical antidepressants) and according to
18 their half-life.

19

20 Materials and methods

21 A pharmacovigilance study was conducted using VigiBase®, the World Health
22 Organization’s Global Individual Case Safety Reports database.¹⁵ VigiBase® stores adverse drug
23 reactions with contributions from national pharmacovigilance programs of more than 130
24 countries. Adverse effects are notified post-marketing by physicians, patients, and

25 pharmaceutical companies. VigiBase® uses the Medical Dictionary for Regulatory Activities
26 (MedDRA) to code adverse effects. In 2021, VigiBase® includes more than 26 million of reports.
27 The database records patient's demographics, reporter's qualification, seriousness of the
28 adverse effect, drugs used at the time of the adverse effect, a causality assessment for each drug
29 and additional information relevant to the case. Observational study using such
30 pharmacovigilance databases can be useful for conducting studies on specific clinical outcomes
31 such as withdrawal syndrome.^{16, 17} A recent study shown that relative risks obtained from meta-
32 analyses of clinical trials and from pharmacovigilance studies are well correlated.¹⁸

33 All reports of patients aged ≥ 6 years old treated with antidepressants among SSRIs,
34 SNRIs and atypical antidepressants registered between January 1st, 1988, and December 31st,
35 2020, were included. SSRIs antidepressants included Paroxetine, Fluvoxamine, Citalopram,
36 Escitalopram, Sertraline and Fluoxetine. SNRIs antidepressants included Duloxetine,
37 Venlafaxine, Milnacipran and Desvenlafaxine. Finally, atypical antidepressants included
38 Reboxetine, Mianserin, Agomelatine, Mirtazapine and Vortioxetine. A case/non-case design was
39 performed (similar to case-control studies), which assesses drug safety by analyzing the
40 disproportionality of adverse drugs reactions reports in pharmacovigilance databases, using
41 logistic regressions to calculate reporting odds ratios (RORs) and their 95% confidence intervals
42 (CIs). Cases were the risk of reporting a withdrawal syndrome coded as "Antidepressant
43 discontinuation syndrome", "Withdrawal syndrome" or "Drug withdrawal syndrome". Non-cases
44 (controls) were all other reports. Reporting Odds Ratios (RORs) are the exposure odds among
45 reported cases of withdrawal syndrome to the exposure odds among reported non-case.

46 Antidepressants were separated into two groups: a short half-lives group (≤ 24 h), and a
47 long half-lives group (> 24 h). First, we compared short half-life antidepressants (including
48 Paroxetine, Fluvoxamine, Duloxetine, Venlafaxine, Milnacipran, Desvenlafaxine, Reboxetine,
49 Mianserin and Agomelatine) and long half-life antidepressants (including Citalopram,
50 Escitalopram, Sertraline, Fluoxetine, Mirtazapine and Vortioxetine). Second, we aimed to better

51 inform clinical practice by comparing these 15 antidepressants for the risk of reporting
52 withdrawal syndrome. As secondary analysis, we include tricyclic antidepressants
53 (Amitriptyline, Clomipramine, Imipramine, Doxepin, Dosulepin, Nortriptyline) to determine if
54 they were associated with a greater risk of reporting a withdrawal syndrome compared to short
55 and long half-life antidepressants.

56 Sensitivity analyses were conducted to assess the robustness of our main analysis,
57 restricting our analysis to physician reports only, to reports from the United States of America
58 only, and to the last 5 years. Patients' informed consent was not necessary since data from
59 Vigibase® were deidentified. The study protocol was registered in the EU-PAS registry
60 (EUPAS41765).

61

62 **Results**

63 In Vigibase®, 15,507 cases among the 338,498 antidepressant reports registered
64 matched the occurrence of a withdrawal syndrome. Cases were mainly women (ratio W/M =
65 2.9), patients aged between 18 and 44 years old (8,562 cases, 55.2%). Reports mainly concerned
66 paroxetine (4,775 cases [30.8%]), venlafaxine (3618 cases [23.3%]), duloxetine (3306 cases
67 [21.3%]) and sertraline (1194 cases [7.7%]). The average time to onset of withdrawal syndrome
68 was shorter for short half-lives (median of one day) than long half-lives (median of two days).

69 The risk of reporting a withdrawal syndrome was higher for patients treated by short
70 half-life antidepressants (ROR 5.38; 95% CI 5.16-5.61) compared to long-half-life
71 antidepressants. Stratification analyses on sex and age suggested that the risk was increased for
72 women (ROR 1.38; 95% CI 1.33-1.43 with men as reference), patients aged 18-44 (ROR 6.86;
73 95% CI 6.17-7.62 with ≥ 75 years old patients as reference) and patients aged 45-64 (ROR 5.1;
74 95% CI 4.58-5.67 with ≥ 75 years old patients as reference). Similar patterns were observed in

75 sensitivity analyses, particularly when restricting data analyses to physicians reports only (ROR
76 4.42; 95% CI 4.04-4.83 concerning short-half-life antidepressants). When compared to tricyclic
77 antidepressants (TCA) in a secondary analysis, the risk of reporting a withdrawal syndrome was
78 higher for short half-life antidepressants (ROR 9.15; 95% CI 8.3-10.09) than long half-life
79 antidepressants (ROR 1.7; 95% CI 1.53-1.88) (as shown in **Table 1**).

80 Paroxetine was associated with a higher risk of reporting a withdrawal syndrome
81 compared to other antidepressants (ROR 3.06; 95% CI 2.95-3.17), followed by Desvenlafaxine
82 (ROR 2.2; 95% CI 2.03-2.38), Venlafaxine (ROR 2.11; 95% CI 2.03-2.19) and Duloxetine (ROR
83 2.01; 95% CI 1.93-2.09). Agomelatine and Vortioxetine were associated with the lowest risks of
84 reporting a withdrawal syndrome (ROR 0.05; 95% CI 0.02-0.10 for Agomelatine an ROR 0.08;
85 95% CI 0.06-0.12 for Vortioxetine) (as shown in **Fig. 1**)

86 **Discussion/Conclusion**

87 Systematic reviews conducted on withdrawal syndromes after SSRIs or SNRIs
88 discontinuation highlighted the methodological weaknesses clinical trials conducted to data.
89 They also mentioned the lack of data concerning sociodemographic characteristics likely to
90 increase the occurrence withdrawal syndromes.^{12, 13, 14, 19} Our comparative study including more
91 than 300,000 patients exposed to antidepressants suggests that patients treated by short half-
92 life antidepressants were twice as likely to report a withdrawal syndrome as patients treated
93 with long half-life antidepressants, especially for 18-65 years old patients, and women. This
94 distribution may be explained by the fact that prescription rules for antidepressants in the
95 elderly and pediatric populations are very different from those in adults. For instance, non-
96 pharmacological treatments take a very important place in the treatment of depressive
97 disorders in the pediatric population. When a pharmacological treatment is necessary, it is
98 widely recommended to start with fluoxetine, a very long half-life antidepressant.²⁰ Concerning
99 elderly populations, dosages are generally reduced compared with adult population.

100 SSRIs and SNRIs were especially known to favor the occurrence of a withdrawal
101 syndrome. This study provides more precise information about the drugs associated with an
102 increased risk of reporting a withdrawal syndrome under real-life conditions of use. Thus,
103 Paroxetine, Desvenlafaxine, Venlafaxine and Duloxetine seemed to be at higher risk of
104 withdrawal syndrome. On the contrary, Agomelatine and Vortioxetine were associated with the
105 lowest risks of reporting a withdrawal syndrome.

106 This study has some limitations which stem from the case-reporting process. For
107 instance, both of Agomelatine and Vortioxetine were marketed recently compared to other
108 drugs. The findings concerning these two drugs need to be confirmed with more perspective in
109 the future. However, restricting this study to a homogeneous therapeutic area (antidepressants)
110 favors the comparison between ROR and risks estimated in meta-analyses.¹⁸ Further studies are
111 needed to confirm these results, although half-life appears to be a key element in preventing the
112 occurrence of a withdrawal syndrome, especially in adult patients. However, other mechanisms,
113 notably pharmacodynamic ones, are certainly involved.^{21, 22} They could help to understand why
114 paroxetine was the only SSRI associated with an increased risk of withdrawal syndrome when
115 compared to all others, and why patients treated with SNRIs are more likely to develop a
116 withdrawal syndrome compared to SSRIs and atypical antidepressants. Our results strengthen
117 recent guidelines which have been published to prevent antidepressant withdrawal syndrome.²³
118 ²⁴ Pending studies, physicians should be aware that paroxetine and SNRIs should be avoided in
119 patients at high risk of withdrawal syndrome.

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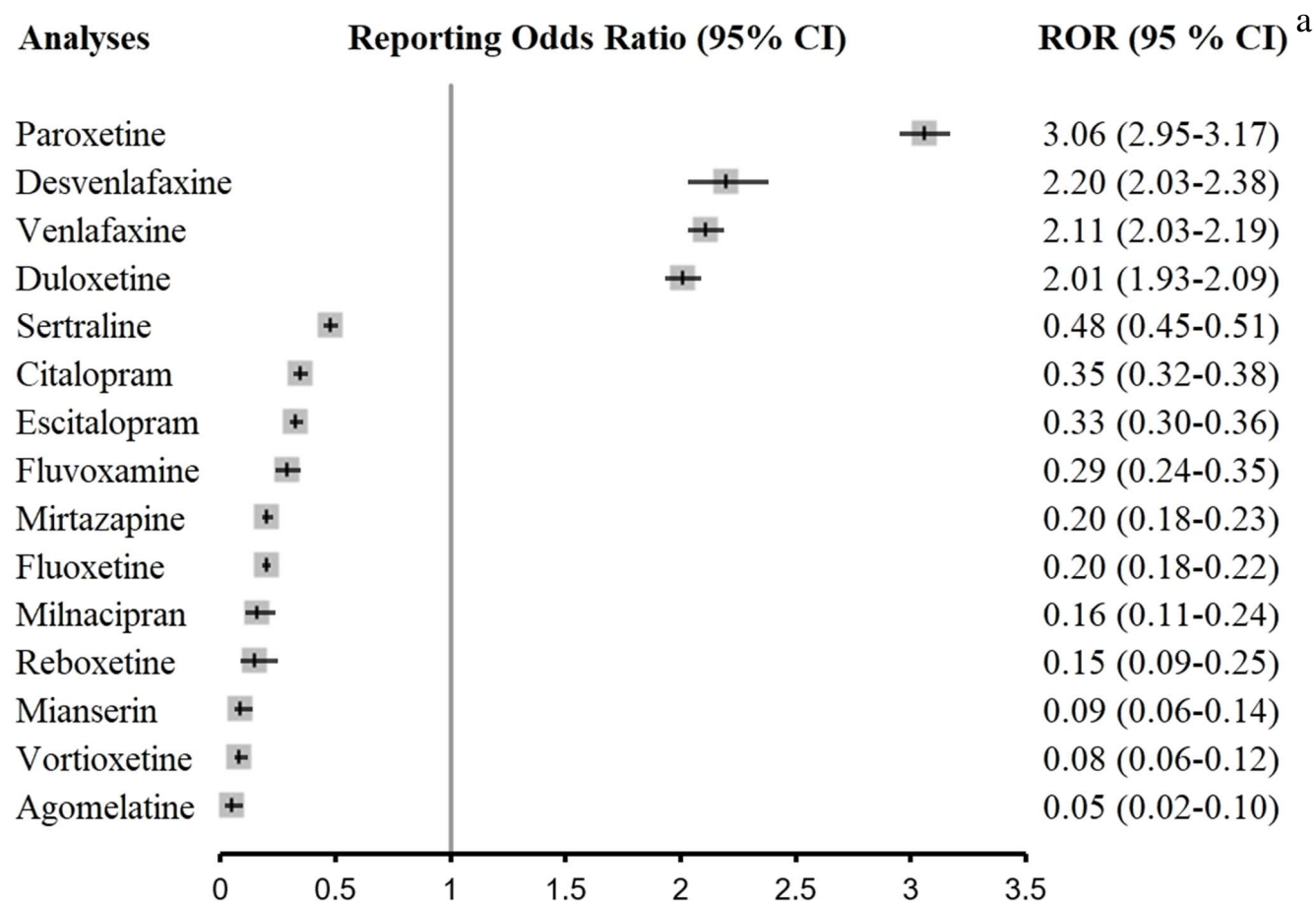
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Figure/Tables Legends

Fig. 1. Forest-plot of the association between the risk of reporting a withdrawal syndrome and 15 common antidepressants.

Table 1. Risk of reporting a withdrawal syndrome for patients treated by SSRIs, SNRIs and atypical antidepressants (main analysis) and TCA (secondary analyses).

Fig. 1. Forest-plot of the association between the risk of reporting a withdrawal syndrome and 15 common antidepressants.



Abbreviations: ROR = Reporting Odds Ratio; CI = confidence interval

^a RORs are the exposure odds among reported cases of withdrawal syndrome to the exposure odds among reported non-cases. We performed logistic regressions to estimate reporting odds ratios with their 95% CI.

Table 1. Risk of reporting a withdrawal syndrome for patients treated by SSRIs, SNRIs and atypical antidepressants (main analysis) and TCA (secondary analyses).

	Cases	Non-cases	ROR (95% CI) ^a
Primary analysis (SSRIs, SNRIs and atypical antidepressants)			
Short half-lives antidepressants ^b *	12,638	145,453	5.38 (5.16-5.61)
Long half-lives antidepressants ^c	2,869	177,538	1 (reference)
Stratification by sex			
Women	11,538	218,987	1.38 (1.33-1.43)
Men	3,969	104,004	1 (reference)
Stratification by age			
6-11 years old	39	1,973	2.02 (1.45-2.82)
12-17 years old	235	9,893	2.42 (2.05-2.86)
18-44 years old	8,562	127,214	6.86 (6.17-7.62)
45-64 years old	5,511	110,143	5.1 (4.58-5.67)
65-74 years old	792	35,375	2.28 (2.01-2.58)
≥ 75 years old	365	37,224	1 (reference)
Sensitivity analyses^d			
Physician reports only			
Short half-lives	2,213	59,014	4.42 (4.04-4.83)
Long half-lives	626	73,861	1 (reference)
USA reports only			
Short half-lives	8,496	57,600	7.05 (6.66-7.46)
Long half-lives	1435	68,544	1 (reference)
From 01.01.2016 to 31.12.2020			
Short half-lives	2,210	35,099	4.5 (4.14-4.9)
Long half-lives	739	52,783	1 (reference)
Secondary analysis			
Short half-lives antidepressants	12,638	145,453	9.15 (8.3-10.09)
Long half-lives antidepressants	2,869	177,538	1.7 (1.53-1.88)
TCA ^e	421	44,343	1 (reference)

Abbreviations: ROR = Reporting Odds Ratios; CI = Confidence Interval; SSRIs = Serotonin Reuptake Inhibitors; SNRIs = Serotonin and Norepinephrine Reuptake Inhibitors; TCA = Tricyclic Antidepressants.

^a RORs are the exposure odds among reported cases of withdrawal syndrome to the exposure odds among reported non-cases. We performed logistic regressions to estimate RORs with their 95% CI.

^b Short half-life antidepressants group includes: Paroxetine, Fluvoxamine, Duloxetine, Venlafaxine, Milnacipran, Desvenlafaxine, Reboxetine, Mianserin and Agomelatine.

^c Long half-life antidepressants group includes: Citalopram, Escitalopram, Sertraline, Fluoxetine, Mirtazapine and Vortioxetine.

^d Sensitivity analyses were conducted to assess the robustness of our results.

^e TCA included in this secondary analysis: Amitriptyline, Clomipramine, Imipramine, Doxepin, Dosulepin, Nortriptyline.

* **eTable 1** in supplementary materials summarizes all the half-lives of the drugs analyzed in this study.