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Short communication

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

Jean-Baptiste Quilichini [a,b], Alexis Revet [b,c], Philippe Garcia [a,b], Régis Bouquié [d], Jacques Hamard [a,b], Antoine Yrondi [e,f,g], François Montastruc [a,b,*]

[a] Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Toulouse University Hospital (CHU), Faculty of Medicine, Toulouse, France
[b] Centre d'Investigation Clinique 1436, Team PEPSS « Pharmacologie En Population cohorteS et biobanqueS », Toulouse University Hospital, France
[c] Department of Child and Adolescent Psychiatry, Faculty of Medicine, Toulouse University Hospital (CHU), Toulouse, France
[d] Laboratoire de Biologie Médicale, Centre Hospitalier Léon-Jean Grégory, avenue du Roussillon, 66330, Thuir, France
[e] Department of Medical Psychiatry, Toulouse University Hospital (CHU), Faculty of Medicine, Toulouse, France
[f] Treatment Resistant Depression Expert Center, FondaMental, Toulouse, France
[g] ToNIC Toulouse NeuroImaging Center, University Paul Sabatier Toulouse, INSERM, Toulouse, France

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ABSTRACT

Background: While case reports and clinical trials reported withdrawal syndrome after reduction and/or discontinuation of antidepressant drugs, no large study has been conducted to compare the risk between the different antidepressants.

Methods: Using data recorded from January 1st, 1988, and December 31st, 2020 in VigiBase®, the World Health Organization's Global Individual Case Safety Reports database, we performed disproportionality analysis to investigate the risk of reporting withdrawal syndrome in patients treated by short half-life antidepressants compared with patients treated by long half-life antidepressants. In addition, we aimed to better inform clinical practice by comparing 15 antidepressants for the risk of reporting withdrawal syndrome.

Results: Among the 338,498 reports with antidepressants of interest, we found 15,507 cases of withdrawal syndrome. Short half-lives antidepressants were associated with an increased risk of reporting a withdrawal syndrome compared to long half-life antidepressants (ROR 5.38; 95% CI 5.16–5.61). The risk was higher for 18–44 years old (ROR 6.88; 95% CI 6.17–7.62), women (ROR 1.38; 95% CI 1.33–1.43) and patients treated with Paroxetine, Desvenlafaxine, Venlafaxine and Duloxetine.

Limitations: The limitations of this study stem from the case-reporting process.

Conclusions: This large observational study in a real-world setting suggests that the use of short half-life antidepressants increases the risk of reporting withdrawal syndrome compared to long half-life antidepressants. Among the most common antidepressants, paroxetine and serotonin-noradrenaline reuptake inhibitors are associated with a greater risk of reporting withdrawal syndrome, while agomelatine and vortioxetine present a lower risk. Additional studies are needed to corroborate our results.

1. Introduction

Several case reports, supported by numerous quantitative studies, have highlighted withdrawal syndromes after antidepressants discontinuation, with physical and psychiatric symptoms appearing after drug discontinuation or decrease. (Fava and Grandi, 1995; Chouinard and Chouinard, 2015; Blum et al., 2008; Phillips, 1995; Pacheco et al., 1996; Debattista and Schatzberg, 1995; Perahia et al., 2005) A systematic review mentions that it would concern on average 56% of the patients treated, with 46% experiencing "severe" symptoms. (Davies and Read, 2019) Some clinical trials have suggested that short half-life antidepressants may have a higher risk of withdrawal syndromes than long half-life antidepressants. (Rosenbaum, 1998; Zajecka et al., 1998; Bogetto et al., 2002) However, these clinical trials had several

* Corresponding author at: Department of Medical and Clinical Pharmacology, Toulouse University Hospital, Faculty of Medicine, Toulouse, France, 37 Allées Jules Guesde, 31000 Toulouse, France.
E-mail address: francois.montastruc@univ-tlse3.fr (F. Montastruc).

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limitations including outcome misclassification, a very limited panel of antidepressants, lack of power. (Van Leeuwen et al., 2021a, 2021b) Moreover, most studies did not use appropriate methods to collect symptoms and distinguish withdrawal syndromes from rebounds and recurrence. Recent systematic reviews also mentioned a lack of epidemiological and socio-demographic data, which could in part be provided by pharmacovigilance databases. (Fava and Coll, 2015) There is therefore a need to further evaluate the risk of withdrawal syndrome in patients taking antidepressants in a large-scale study including the most common antidepressants under everyday life conditions. Here, we compared the risk of reporting withdrawal syndrome between 15 antidepressants (Selective Serotonin Reuptake Inhibitors [SSRIs], Serotonin and Norepinephrine Reuptake inhibitors [SNRIs], and atypical antidepressants) and according to their half-life.

2. Materials and methods

A pharmacovigilance study was conducted using VigiBase®, the World Health Organization's Global Individual Case Safety Reports database. (VigiBase 2021) VigiBase® stores adverse drug reactions with contributions from national pharmacovigilance programs of more than 130 countries. Adverse effects are notified post-marketing by physicians, patients, and pharmaceutical companies. VigiBase® uses the Medical Dictionary for Regulatory Activities (MedDRA) to code adverse effects. In 2021, VigiBase® includes more than 26 million of reports. The database records patient's demographics, reporter's qualification, seriousness of the adverse effect, drugs used at the time of the adverse effect, a causality assessment for each drug and additional information relevant to the case. Observational study using such pharmacovigilance databases can be useful for conducting studies on specific clinical outcomes such as withdrawal syndrome. (Faillie, 2019; Pradhan et al., 2020) A recent study shown that relative risks obtained from meta-analyses of clinical trials and from pharmacovigilance studies are well correlated. (Khouri et al., 2021)

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

Antidepressants were separated into two groups: a short half-lives group (≤ 24 h), and a long half-lives group (> 24 h). First, we compared short half-life antidepressants (including Paroxetine, Fluvoxamine, Duloxetine, Venlafaxine, Milnacipran, Desvenlafaxine, Reboxetine, Mianserin and Agomelatine) and long half-life antidepressants (including Citalopram, Escitalopram, Sertraline, Fluoxetine, Mirtazapine and Vortioxetine). Second, we aimed to better inform clinical practice by comparing these 15 antidepressants for the risk of reporting withdrawal syndrome. As secondary analysis, we include tricyclic antidepressants (Amitriptyline, Clomipramine, Imipramine, Doxepin, Dosulepin, Nortriptyline) to determine if they were associated with a greater risk of reporting a withdrawal syndrome compared to short and long half-life antidepressants.

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

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]	2869	177,538	1 (reference)
Stratification by sex			
Women	11,538	218,987	1.38 (1.33–1.43)
Men	3969	104,004	1 (reference)
Stratification by age			
6–11 years old	39	1973	2.02 (1.45–2.82)
12–17 years old	235	9893	2.42 (2.05–2.86)
18–44 years old	8562	127,214	6.86 (6.17–7.62)
45–64 years old	5511	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	2213	59,014	4.42 (4.04–4.83)
Long half-lives	626	73,861	1 (reference)
USA reports only			
Short half-lives	8496	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	2210	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	2869	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.

3. Results

In VigiBase®, 15,507 cases among the 338,498 antidepressant reports registered matched the occurrence of a withdrawal syndrome. Cases were mainly women (ratio W/M = 2.9), patients aged between 18 and 44 years old (8562 cases, 55.2%). Reports mainly concerned

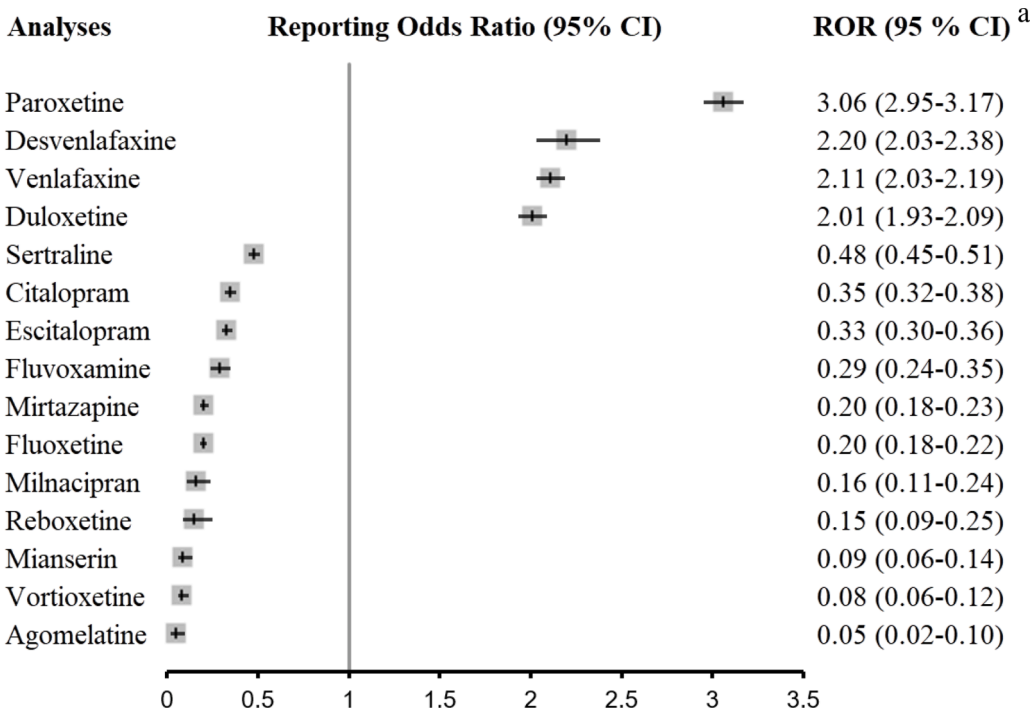

Fig. 1. Forest-plot of the association between the risk of reporting a withdrawal syndrome and 15 common antidepressants. Abbreviations: ROR = Reporting Odds Ratio; CI = confidence interval. [a] RORs are the exposure odds among reported cases of withdrawal syndrome to the exposure odds among reported non-cases. We performed logistic regressions to estimate reporting odds ratios with their 95% CI.

paroxetine (4775 cases [30.8%]), venlafaxine (3618 cases [23.3%]), duloxetine (3306 cases [21.3%]) and sertraline (1194 cases [7.7%]). The average time to onset of withdrawal syndrome was shorter for short half-lives (median of one day) than long half-lives (median of two days).

The risk of reporting a withdrawal syndrome was higher for patients treated by short half-life antidepressants (ROR 5.38; 95% CI 5.16–5.61) compared to long-half-life antidepressants. Stratification analyses on sex and age suggested that the risk was increased for women (ROR 1.38; 95% CI 1.33–1.43 with men as reference), patients aged 18–44 (ROR 6.86; 95% CI 6.17–7.62 with $\geq$ 75 years old patients as reference) and patients aged 45–64 (ROR 5.1; 95% CI 4.58–5.67 with $\geq$ 75 years old patients as reference). Similar patterns were observed in sensitivity analyses, particularly when restricting data analyses to physicians reports only (ROR 4.42; 95% CI 4.04–4.83 concerning short-half-life antidepressants). When compared to tricyclic antidepressants (TCA) in a secondary analysis, the risk of reporting a withdrawal syndrome was higher for short half-life antidepressants (ROR 9.15; 95% CI 8.3–10.09) than long half-life antidepressants (ROR 1.7; 95% CI 1.53–1.88) (as shown in **Table 1**).

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

4. Discussion/Conclusion

Systematic reviews conducted on withdrawal syndromes after SSRIs or SNRIs discontinuation highlighted the methodological weaknesses clinical trials conducted to data. They also mentioned the lack of data concerning sociodemographic characteristics likely to increase the occurrence withdrawal syndromes. (Van Leeuwen et al., 2021a, 2021b; Fava and Coll, 2015; 2018) Our comparative study including more than 300,000 patients exposed to antidepressants suggests that patients treated by short half-life antidepressants were twice as likely to report a withdrawal syndrome as patients treated with long half-life antidepressants, especially for 18–65 years old patients, and women. This distribution may be explained by the fact that prescription rules for antidepressants in the elderly and pediatric populations are very different from those in adults. For instance, non-pharmacological treatments take a very important place in the treatment of depressive disorders in the pediatric population. When a pharmacological treatment is necessary, it is widely recommended to start with fluoxetine, a very long half-life antidepressant. (Hetrick et al., 2021) Concerning elderly populations, dosages are generally reduced compared with adult population.

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

This study has some limitations which stem from the case-reporting process. For instance, both of Agomelatine and Vortioxetine were marketed recently compared to other drugs. The findings concerning these two drugs need to be confirmed with more perspective in the future. However, restricting this study to a homogeneous therapeutic area (antidepressants) favors the comparison between ROR and risks estimated in meta-analyses. (Khouri et al., 2021) Further studies are needed to confirm these results, although half-life appears to be a key element in preventing the occurrence of a withdrawal syndrome, especially in adult patients. However, other mechanisms, notably pharmacodynamic ones, are certainly involved. (Blier and Tremblay, 2006; Fava and Cosci, 2019) They could help to understand why paroxetine was the only SSRI associated with an increased risk of withdrawal syndrome when compared to all others, and why patients treated with SNRIs are more likely to develop a withdrawal syndrome compared to SSRIs and

atypical antidepressants. Our results strengthen recent guidelines which have been published to prevent antidepressant withdrawal syndrome. (Royal College of Psychiatrist, 2021; Horowitz and Taylor, 2019) Pending studies, physicians should be aware that paroxetine and SNRIs should be avoided in patients at high risk of withdrawal syndrome.

CRediT authorship contribution statement

Jean-Baptiste Quilichini: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Alexis Revet:** Writing – review & editing. **Philippe Garcia:** Writing – review & editing. **Régis Bouquié:** Writing – review & editing. **Jacques Hamard:** Writing – review & editing. **Antoine Yrondi:** Writing – review & editing. **François Montastruc:** Conceptualization, Formal analysis, Supervision.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Statement of Ethics

Patients' informed consent was not necessary since data from VigiBase® were deidentified. The study protocol was registered in the EU-PAS registry (EUPAS41765).

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The work was performed during the university research time of the authors using the database which is available without fees in the department of the authors

Author Contributions

Dr. Montastruc had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design

Jean-Baptiste Quilichini and François Montastruc

Acquisition, analysis, or interpretation of data

All authors.

Drafting of the manuscript

Jean-Baptiste Quilichini

Critical revision of the manuscript for important intellectual content

All authors.

Statistical analysis

Jean-Baptiste Quilichini and Philipe Garcia

Supervision

François Montastruc

Data Availability Statement

No additional data available. For legal and ethical reasons, individual-level patient data cannot be shared by the authors and are only accessible to authorized researchers after application to the Uppsala monitoring center.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.10.041.

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