Withdrawal syndrome following discontinuation of 28 antidepressants: pharmacovigilance analysis of 31,688 reports from the WHO spontaneous reporting database- Drug Safety

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Electronic Supplementary Material (ESM)

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Additional Methods

Data source: the Vigibase®

The WHO Programme for International Drug Monitoring (WHO PIDM) was established in 1968 as a result of the thalidomide crisis of the early 1960s. WHO PIDM currently has around 140 member countries (November 2020). In each participating country, the ministry of health, or equivalent, has appointed a national centre for pharmacovigilance that collects and manages Individual Case Safety Reports (ICSR) and is the national point of contact. These reports are transferred electronically to VigiBase®, the WHO global database of ICSRs ('report' denotes ICSR in this document) [1]. VigiBase® is maintained and developed by the UMC and members of the WHO PIDM can access and analyse this common resource using VigiLyze®, a signal detection and management tool provided by UMC.

Each ICSR includes anonymous administrative data (the country, the reporter's qualification, and a completeness score), patient information (age and gender), and information on medications (international non-proprietary name or trade name, anatomical therapeutic chemical [ATC] classification,[2] indication, date of onset, date of withdrawal, dosage, administration route, and adverse events coded according to the Medical Dictionary for Regulatory Activities version 23.1 [MedDRA®]) [3]. If a medication is considered to be probably responsible for the adverse event, it is defined as "suspect" or "interacting". If not, it is defined as "concomitant". Detailed information on the items contained in ICSRs are described on the UMC website [4]. According to WHO policy and the UMC's guidelines, ICSRs sent from member countries to VigiBase® are anonymized.

Study design

Search strategy to identify cases

Cases of withdrawal syndrome were identified by searching for the preferred terms (PT) "withdrawal syndrome", "antidepressants discontinuation syndrome" and the sub-Standardized MedDRA Queries (sub-SMQs) "drug withdrawal".[3] We included reports involving the following 28 antidepressants: amitriptyline, nortriptyline, desipramine, imipramine, clomipramine, doxepin, lofepramine, fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram, mianserin, trazodone, nefazodone, mirtazapine, bupropion, venlafaxine, milnacipran, reboxetine, duloxetine, agomelatine, desvenlafaxine, vortioxetine, esketamine, hypericum perforatum and vilazodone. Antidepressants were classified as tricyclics (TCAs) (ATC: N06AA; amitriptyline, clomipramine, imipramine, doxepin, nortriptyline, desipramine, lofepramine), SSRIs (ATC: N06AB; paroxetine, sertraline, fluoxetine, citalopram, escitalopram, fluvoxamine), and other or "newer" antidepressants (ATC: N06AX; duloxetine, venlafaxine, desvenlafaxine, bupropion, mirtazapine, trazodone, nefazodone, vortioxetine, vilazodone, milnacipran, mianserin, reboxetine, hypericum perforatum, agomelatine, esketamine), based on the Anatomical Therapeutic Chemical (ATC) classification system [2].

Exclusion criteria

We excluded ICSRs concerning patients under 12 years of age as the use of antidepressants in childhood is controversial and in most of the cases off-label [5]. New-borns were also excluded as they suffer from neonatal withdrawal syndrome as a result of exposure during pregnancy or breast feeding. In terms of underlying mechanisms of pathophysiology and clinical features, this is a different clinical entity that deserves separate attention and has previously been addressed and characterized [6].

Statistical analyses

We provided descriptive statistics on demographic and clinical characteristics of reported cases. We provided frequencies and percentages for sex, country of origin, number of serious reactions, number of cases with other psychotropic medications. Means and standard deviations were provided for age, dose, duration of treatment and duration of the reaction. Mean doses were provided in mg for each single drug and as for antidepressants overall we calculated the mean overall dose based on the defined daily dose or DDD [7].

Two different disproportionality approaches were performed to increase consistency and robustness of findings. We estimated the reporting odds ratio (ROR) [8, 9], and the Bayesian information component (IC) [10], for all AEs with threat least four reports using the R packages PhViD and BCPNN. The ROR is the odds of

exposure to a specific drug among the cases divided by the odds of exposure to the same drug in the non-cases [8, 9, 11]. The IC is a shrinkage-based measure of observed-to-expected disproportionality [12]. Higher ROR/IC estimates reflect stronger disproportion. Ninety-five percent confidence intervals (CIs) were estimated for both ROR and IC. The ROR was deemed statistically significant if the lower limit of the CI is >1,[8] for IC, when the lower limit of CI of the IC is >0.10.

The ROR (also known as frequentist method) is largely used because it is relatively easy to understand, interpret and compute for clinicians (it is based on the same principles of calculation using the 2x2 table). This statistical measure expresses the extent to which the reported AE is associated with the suspected drug compared with the other drugs in the database. The occurrence of AEs related to other drugs in the database is used as a proxy for the background incidence of AEs (the denominator is unknown in pharmacovigilance). Conversely, IC is a Bayesian method based on Bayes' law to estimate the probability (posterior probability) that the suspected event occurs given the use of suspect drug.

Although several studies have examined and compared the performance of different algorithms, the accuracy in terms of sensitivity, specificity, and early identification of safety issues is largely comparable, especially when the number of cases (AEs) is more than 3. Therefore, there is no recognized gold standard methodology [13]. In other words, the choice of a disproportionality statistical approach does not appreciably affect the performance in terms of signal detection, and the absolute performance depends on the database size and features, as well as the level of confounding. When the level of confounding increases and/or the effect sizes become larger, Bayesian approaches may be preferable [14]. Overall, the performance of studies using disproportionality algorithms is noteworthy (i.e., the capacity to discriminate true from false positive drug–event associations), especially for adverse events with low/rare background incidence and a likely drug-attributable component such as torsade de pointes. Notably, large concordance was demonstrated between disproportionality measures (ROR) and relative risks emerged in formal analytical studies for a set of known AEs, thus providing a rough indication of the clinical significance of the signal strength [15].

For these reasons we have used two different approaches for signal detection, to increase the robustness of findings and reduce the likelihood of false positives; in our study, both methods were used for signal detection, and when the two disproportionality measures for a given AE met the criteria for statistical significance a safety signal for the AE was considered.

Serious vs non-serious reactions

We performed secondary analyses between serious and non-serious reports of withdrawal syndrome. The following characteristics were considered: age (both as a continuous and dichotomous variable, i.e., adolescents <18 years and adults $\geq$18), sex (female and male), antidepressant dose (as mean and standard deviation (SD) of the defined daily dose (DDD)),[2] treatment duration (mean and SD in months), duration of the withdrawal syndrome (mean and SD in days) and type of concomitant therapy. As concomitant therapies, we considered other psychotropic drugs, and cases were grouped as cases with mood stabilizers, with benzodiazepines, with other antidepressants and with antipsychotics. We also considered the number of concomitant psychotropics drugs, grouping cases in cases with >2, >3 or >4 comedications.

Identification of the clinical symptoms of the withdrawal syndrome

To identify the most commonly reported symptoms and signs of antidepressant-related withdrawal syndrome we selected only cases with one suspected drug, i.e. the suspected antidepressant. This approach was employed to minimize the risk of confounders due to co-suspected drugs, assuring that the co-reported symptoms were associated only with the suspected antidepressant and not with other co-reported psychotropic or non-psychotropic medications. Symptoms and signs were reported with absolute numbers (n) and frequency of reporting (%).

Table 1. Criteria for the classification and prioritisation of relevant disproportionality signals

Clinical priority features for each drug	2 points	1 point	0 point
Number of cases of withdrawal syndrome/Total number of reports of any AE	>10%	5-10%	0-4%:

Number of cases of withdrawal syndrome without confounders/number of all cases of withdrawal	>71%	51-70%	≤50%
Significant ROR and IC- consistent across different analyses (in the main analysis, in the intraclass analysis and with buprenorphine as a comparator)	ROR and IC significant in all three analyses	ROR and IC significant in two analyses	ROR and IC significant one analysis
Magnitude of the lower limit of the 95% CI of the ROR	..	>10	0-10

AEs: adverse events; IC: information component; ROR: reporting odds ratio.

Confounders were defined as all drugs that can cause withdrawal syndrome, i.e., other psychotropic drugs (such as other antidepressants, antipsychotics, benzodiazepines), opioids, any other substance of abuse. Antidepressants with statistically significant disproportionate reporting were ranked based on a semiquantitative score assessing four different items. Based on computed scores of 0–1, 2-5 or 6-7, we classified respectively antidepressants as having potentially weak (green light), moderate (yellow light) or strong (red light) association with withdrawal syndrome

Table 2. Mean prescribed dose for each antidepressant

Drug	**n of cases**	**Mean dose ± sd (mg)**
Agomelatine	12	37.5 ± 13.36
Amitriptyline	251	264.5 + 113.34
Bupropion	551	180.3 ±212.96
Citalopram	646	22.81 ± 14.52
Clomipramine	143	85.59 ± 68.08
Desipramine	33	142.2 ± 101.45
Desvenlafaxine	1,676	64.95 ± 36.48
Doxepin	71	67.10 ±68.07
Duloxetine	8,535	50.73+23.3
Escitalopram	535	12.41 ± 8.38
Esketamine	5	56.25 ± 37.72
Fluoxetine	749	18.4 7.72
Fluvoxamine	122	117.3 ± 94.88
Imipramine	76	117.9 ± 77.40
Lofepramine	8	105.25 ± 89.98
Mianserin	31	29.25 ± 27.44
Mirtazapine	270	29.97 + 29.54
Nefazodone	121	298.3 ± 168.67
Nortriptyline	56	56.34 ± 56.34
Reboxetine	17	5.32 ± 2.92
Paroxetine	9,899	5.25 ± 9.14
Sertraline	1,757	43.32 ± 27.96
Trazodone	167	140.50 ± 112.72
Venlafaxine	5,861	119.8 ± 97.31
Vilazodone	47	25.27 ± 14.59
Vortioxetine	49	11.67 ± 6.41

n of cases: number of cases of withdrawal syndrome; sd: standardized deviation; mg: milligrams.

Note: this was calculated based on the cases that reported the dose (n).

Table 3. Reporting odds ratios (ROR) and information components (IC) for withdrawal Antidepressants-related withdrawal syndrome by class of antidepressant and for each antidepressant using buprenorphine as a positive control

Drug	n cases	n non-cases	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI
Antidepressants	31,846	600,050	1.45	1.4	1.51	0.05	0.03	0.06
Tricyclics	667	64,091	0.29*	0.26	0.31	-1.24*	-1.37	-1.15
SSRIs	14,050	276,560	1.39	1.34	1.45	0.09	0.06	0.11
Newer	17,659	279,014	1.73	1.67	1.81	0.13	0.11	0.15
Tricyclics								
Amitriptyline	261	3,384	0.24*	0.21	0.27	-1.71*	-1.91	-1.56
Clomipramine	150	9,539	0.43*	0.37	0.51	-1.09*	-1.36	-0.89
Imipramine	84	5,473	0.42*	0.34	0.52	-1.16*	-1.52	-0.9
Doxepin	74	6,333	0.32*	0.25	0.4	-1.53*	-1.92	-1.25
Nortriptyline	69	7,512	0.25*	0.2	0.32	-1.85*	-2.25	-1.56
Desipramine	34	2,450	0.38*	0.27	0.53	-1.32*	-1.89	-0.91
Lofepramine	8	3,314	0.07*	0.03	0.13	-3.74*	-4.95	-2.94
SSRIs								
Paroxetine	10,074	60,069	4.6	4.41	4.8	0.76	0.73	0.78
Sertraline	1,900	70,754	0.74*	0.69	0.78	-0.24*	-0.32	-0.18
Fluoxetine	853	71,982	0.32*	0.3	0.35	-1.05*	-1.16	-0.97
Citalopram	670	35,771	0.51*	0.47	0.56	-0.71*	-0.84	-0.62
Escitalopram	590	32,499	0.5*	0.46	0.54	-0.76*	-0.9	-0.66
Fluvoxamine	130	9,771	0.36*	0.31	0.44	-1.32*	-1.61	-1.11
Other antidepressants								
Duloxetine	8,583	56,620	4.16	3.98	4.34	0.76	0.72	0.79
Venlafaxine	6,203	57,065	2.98	2.85	3.12	0.65	0.61	0.68
Desvenlafaxine	1,701	16,121	2.89	2.72	3.08	1.06	0.98	1.12
Bupropion	566	63,236	0.25*	0.22	0.27	-1.42*	-1.56	-1.32
Mirtazapine	306	26,755	0.31*	0.28	0.35	-1.37*	-1.56	-1.23
Trazodone	230	19,235	0.33*	0.29	0.38	-1.38*	-1.6	-1.22
Nefazodone	126	8,600	0.4*	0.34	0.48	-1.2*	-1.49	-0.99
Vortioxetine	60	13,363	0.12*	0.1	0.16	-2.78*	-3.21	-2.47
Vilazodone	55	4,843	0.31*	0.24	0.41	-1.58*	-2.03	-1.26
Milnacipran	40	4289	0.26*	0.19	0.35	-1.86*	-2.39	-1.48
Mianserin	35	7,173	0.13*	0.1	0.19	-2.74*	-3.3	-2.34
Reboxetine	21	2,184	0.26*	0.17	0.41	-1.83*	-2.56	-1.32
Hypericum perforatum	17	2,177	0.21*	0.13	0.35	-2.12*	-2.94	-1.55
Agomelatine	12	3,633	0.09*	0.05	0.16	-3.31*	-4.29	-2.64
Esketamine	5	1,270	0.11*	0.04	0.26	-3.02*	-4.58	-2.04

*: not significant.

CI: confidence interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio; SSRI: selective serotonin reuptake inhibitors.

Table 4. Disproportionality intraclass analysis for TCAs

Drug	n cases	n non-cases	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI

Amitriptyline	261	30,667	0.71*	0.61	0.83	-0.27*	-0.46	-0.11
Clomipramine	150	9,689	1.66	1.38	1.99	0.59	0.35	0.81
Imipramine	84	5,557	1.54	1.23	1.94	0.55	0.22	0.84
Doxepin	74	6,407	1.14*	0.89	1.45	0.16*	-0.18	0.47
Nortriptyline	69	7,581	0.87*	0.68	1.12	-0.18*	-0.54	0.14
Desipramine	34	2,484	1.35*	0.95	1.91	0.40*	-0.12	0.85
Lofepramine	8	3,322	0.22*	0.11	0.45	-2.03*	-3.20	-1.20

*: not significant.

CI: confidence interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio.

Table 5. Disproportionality intraclass analysis for SSRIs

Drug	n cases	n non-cases	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI
Paroxetine	10,074	70,143	9.13	8.79	9.48	1.57	1.54	1.60
Sertraline	1,900	72,654	0.45*	0.43	0.48	-0.89*	-0.95	-0.82
Fluoxetine	853	72,835	0.18*	0.17	0.20	-2.04*	-2.14	-1.95
Citalopram	670	36,441	0.34*	0.31	0.36	-1.39*	-1.51	-1.29
Escitalopram	590	33,089	0.33*	0.30	0.36	-1.44*	-1.56	-1.32
Fluvoxamine	130	9,901	0.25*	0.21	0.30	-1.88*	-2.14	-1.64

*: not significant.

CI: confidence interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio; SSRI: selective serotonin reuptake inhibitors.

Table 6. Disproportionality intraclass analysis for other antidepressants

Drug	n cases	n non-cases	ROR	Lower 95%CI	Upper 95%CI	IC	Lower 95%CI	Upper 95%CI
Duloxetine	8,583	65,203	3.71	3.60	3.83	1.14	1.11	1.18
Venlafaxine	6,203	63,268	2.11	2.04	2.17	0.72	0.68	0.76
Desvenlafaxine	1,701	17,822	1.74	1.65	1.83	0.68	0.61	0.75
Bupropion	566	63,802	0.11*	0.10	0.12	-2.75*	-2.87	-2.63
Mirtazapine	306	27,061	0.17*	0.15	0.19	-2.39*	-2.56	-2.24
Trazodone	230	19,465	0.18*	0.16	0.20	-2.33*	-2.52	-2.15
Nefazodone	126	8,726	0.23*	0.19	0.27	-2.04*	-2.30	-1.80
Vortioxetine	60	13,423	0.07*	0.05	0.09	-3.72*	-4.11	-3.38
Vilazodone	55	4,898	0.18*	0.14	0.23	-2.40*	-2.80	-2.04
Milnacipran	40	4,329	0.15*	0.11	0.20	-2.67*	-3.15	-2.26
Mianserin	35	7,208	0.08*	0.05	0.10	-3.60*	-4.11	-3.16
Reboxetine	21	2,205	0.15*	0.10	0.23	-2.62*	-3.30	-2.06
Hypericum perforatum	17	2,194	0.12*	0.08	0.20	-2.91*	-3.67	-2.30
Agomelatine	12	3,645	0.05*	0.03	0.09	-4.12*	-5.05	-3.42
Esketamine	5	1,275	0.06*	0.03	0.15	-3.80*	-5.32	-2.80

*: not significant.

CI: confidence interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio.

Table 7. Evaluation and classification of relevant disproportionality signals

Drug	n cases	CRITERION 1		CRITERION 2		CRITERION 3				CRITERION 4		TOTAL SCORE	Priority level
		n cases / total n AEs	SCORE	n cases without confounders/ n cases	SCORE	Significance across analyses			SCORE	Magnitude of ROR lower 95%CI	SCORE		
						Main	Intraclass	vs. buprenorphine					
Paroxetine	10,074	14%	2	86%	2	yes	yes	yes	2	44.07	1	7	
Duloxetine	8,583	13%	2	78%	2	yes	yes	yes	2	39.78	1	7	
Venlafaxine	6,203	10%	1	79%	2	yes	yes	yes	2	28.43	1	6	
Desvenlafaxine	1,701	10%	1	74%	2	yes	yes	yes	2	26.96	1	6	
Clomipramine	150	2%	0	71%	2	yes	yes	no	1	3.60	0	3	
Sertraline	1,900	3%	0	77%	2	yes	no	no	0	6.89	0	2	
Citalopram	670	2%	0	72%	2	yes	no	no	0	4.66	0	2	
Imipramine	84	2%	0	55%	1	yes	yes	No	1	3.32	0	2	
Vilazodone	55	1%	0	73%	2	yes	no	no	0	2.34	0	2	
Fluoxetine	853	1%	0	63%	1	yes	no	no	0	2.98	0	1	
Escitalopram	590	2%	0	65%	1	yes	no	no	0	4.50	0	1	
Bupropion	566	1%	0	50%	1	yes	no	no	0	2.21	0	1	
Doxepin	74	1%	0	51%	1	yes	no	no	0	2.5	0	1	
Mirtazapine	306	1%	0	56%	1	yes	no	no	0	2.75	0	1	
Fluvoxamine	130	1%	0	64%	1	yes	no	no	0	3.01	0	1	
Nefazodone	126	1%	0	63%	1	yes	no	no	0	3.30	0	1	
Nortriptyline	69	1%	0	46%	0	yes	no	no	1	1.95	0	1	
Amitriptyline	261	1%	0	44%	0	yes	no	no	0	2.04	0	0	
Trazodone	230	1%	0	0%	0	yes	no	no	0	2.82	0	0	
Milnacipran	40	1%	0	43%	0	yes	no	no	0	1.84	0	0	
Desipramine	34	1%	0	47%	0	yes	no	no	0	2.66	0	0	
Reboxetine	21	1%	0	48%	0	yes	no	no	0	1.68	0	0	

AEs=adverse events; CI=confidence interval; n cases: number of cases of withdrawal syndrome; total n AEs: number of all adverse events; ROR: reporting odds ratio.

Table 8. Symptoms reported in association with withdrawal reaction

Symptoms	N	Frequency %
Dizziness	2,731	13.13
Nausea	1,972	9.48
Paraesthesia	1,726	8.30
Headache	1,529	7.35
Anxiety	1,189	5.72
Feeling abnormal	971	4.67
Suicidal ideation	969	4.66
Insomnia	853	4.10
Depression	826	3.97
Fatigue	772	3.71
Tremor	761	3.66
Hyperhidrosis	744	3.58
Agitation	663	3.19
Vomiting	629	3.02
Vertigo	608	2.92
Malaise	593	2.85
Confusional state	587	2.82
Disturbance in attention	564	2.71
Crying	554	2.66
Irritability	538	2.59
Nightmare	538	2.59
Diarrhoea	521	2.51
Aggression	506	2.43
Tinnitus	437	2.10
Weight increased	420	2.02
Influenza like illness	392	1.88
Anger	389	1.87
Nervousness	357	1.72
Pain	350	1.68
Dependence	348	1.67
Asthenia	341	1.64
Abnormal dreams	316	1.52
Memory impairment	313	1.50
Sleep disorder	296	1.42
Palpitations	285	1.37
Mood swings	280	1.35
Panic attack	255	1.23
Vision blurred	243	1.17
Visual impairment	239	1.15
Emotional disorder	229	1.10
Migraine	224	1.08
Hypoaesthesia	220	1.06
Balance disorder	215	1.03
Lethargy	214	1.03

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