

Antipsychotic-related DRESS syndrome:

analysis of individual case safety reports of the WHO pharmacovigilance database

Running title: Antipsychotic-related DRESS in VigiBase®

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The number of tables, figures, and references, the number of words in the Abstract and Manuscript and the number of supplementary figures and tables

number of words in the abstract: 250/250 (including headings)

number of key points: 3/3

number of words in the manuscript: (excluding tables and legends to figures): 3,787/6,000

number of figures: 1

number of tables: 4

number of references: 85

number of supplementary tables: 4

Electronic Supplementary Material

Supplementary Table 1. List of all 82 typical and atypical antipsychotic agents according to the WHO Anatomical Therapeutic Chemical (ATC) index included in the analysis.

Typical antipsychotics	acepromazine, acetophenazine, benperidol, bromperidol, butaperazine, carfenazine, chlorproethazine, chlorpromazine, chlorprothixene, clopenthixol, cyamemazine, dixyrazine, droperidol, fluanisone, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, lenperone, loxapine, mesoridazine, metitepine, molindone, moperone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, piperacetazine, pipotiazine, prochlorperazine, promazine, prothipendyl, spiperone, sulforidazine, thiopropazate, thioproperazine, thioridazine, thiothixene, timiperone, trifluoperazine, trifluoperidol, triflupromazine, zuclopenthixol.
Atypical antipsychotics	amoxapine, amisulpride, aripiprazole, asenapine, blonanserin, brexpiprazole, cariprazine, caripramine, clocapramine, clorotepine, clotiapine, clozapine, iloperidone, levosulpiride, lumateperone, lurasidone, melperone, mosapramine, nemonapride, olanzapine, paliperidone, perospirone, quetiapine, remoxipride, reserpine, risperidone, sertindole, sulpiride, sultopride, tiapride, veralipride, ziprasidone, zotepine.

Supplementary Table 2. Criteria for the classification and prioritization of relevant disproportionate reporting.

Clinical priority features for each drug	2 points	1 point	0 point
Number of cases of DRESS syndrome/Total number of reports of any AE*	>0.4%	0.1-0.4%	<0.1%:
Number of cases of DRESS syndrome without confounders**/number of all cases of DRESS	>10%	10-1%	<1%
Significant ROR and IC values consistent across different analyses (in the main analysis, in the intraclass analysis and with carbamazepine 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	NA	>1	0-1

AEs: adverse events; DRESS: drug reaction with eosinophilia and systemic symptoms; IC: information component; NA: Not applicable; ROR: reporting odds ratio.

*This criterion has been adapted as this is a rare AE.

** Cases with confounders were cases in which other drugs known to have the potential to cause DRESS were co-prescribed. Drugs considered included: Amoxicillin, Allopurinol, Azithromycin, Carbamazepine, Ceftriaxone, Dapsone, Ibuprofen, Lamotrigine, Levetiracetam, Minocycline, Phenobarbital, Phenytoin, Piperacillin, Rifampicin, Ramipril, Sulfamethoxazole, Sulfasalazine, Tazobactam, Topiramate, Trimethoprim, Vancomycin, Valproate.

Supplementary Table 3. Reporting odds ratios (RORs) and 95% confidence intervals (CI) for each antipsychotic (ROR > 1 indicates an increased DRESS syndrome reporting associated with antipsychotics) – antipsychotics intraclass comparison.

Medication	n DRESS	n ADR	ROR	Lower 95% ROR	Higher 95% ROR	IC	Lower 95% IC	Higher 95% IC
Typical Antipsychotics								
Haloperidol	57	35,870	0.88	0.64	1.21	0.32	-0.12	0.64
Chlorpromazine	37	12,636	1.89*	1.31	2.72	0.92*	0.37	1.31
Cyamemazine	23	5,188	2.82*	1.82	4.37	1.38*	0.68	1.87
Levomepromazine	13	5,368	1.44	0.82	2.53	0.54	-0.40	1.18
Loxapine	11	3,775	1.74	0.94	3.20	0.76	-0.26	1.45
Zuclopenthixol	11	4,359	1.50	0.81	2.76	0.58	-0.44	1.27
Perphenazine	6	3,323	1.05	0.46	2.37	0.10	-1.32	1.01
Droperidol	5	2,197	1.33	0.55	3.24	0.39	-1.17	1.37
Atypical Antipsychotics								
Clozapine	800	184,094	4.23*	3.76	4.76	1.47*	1.35	1.55
Olanzapine	152	71,859	1.03	0.87	1.22	0.21	-0.06	0.40
Quetiapine	134	87,822	0.71	0.59	0.85	-0.23	-0.52	-0.02
Risperidone	89	114,334	0.33	0.27	0.41	-1.14	-1.49	-0.89
Aripiprazole	61	70,082	0.39	0.30	0.51	-1.07	-1.49	-0.76
Lurasidone	23	13,145	0.85	0.56	1.28	-0.20	-0.90	0.29
Ziprasidone	23	14,911	0.75	0.49	1.13	-0.37	-1.07	0.12
Amisulpride	16	7,725	1.01	0.62	1.65	0.03	-0.81	0.61
Paliperidone	12	47,633	0.11	0.06	0.20	-2.87	-3.85	-2.20
Sulpiride	7	4,861	0.70	0.33	1.47	-0.47	-1.77	0.38
Tiapride	7	1,922	1.78	0.85	3.75	0.76	-0.54	1.61

ADR: Adverse drug reaction; DRESS: Drug reaction with eosinophilia and systemic symptoms; n: number. *significant

Supplementary Table 4. Clinical classification and prioritization of relevant disproportionate reporting.

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/ total n cases DRESS	SCORE	Significance across analyses			SCORE	Magnitude of ROR lower 95%CI	SCORE		
						Main	Intraclass	vs. carbamazepine					
Clozapine	800	0.43%	2	58.99%	2	yes	yes	no	1	2.1	1	6	
Chlorpromazine	37	0.29%	1	2.73%	1	yes	yes	no	1	1.1	1	4	
Cyamemazine	23	0.44%	2	1.70%	1	yes	yes	no	1	1.5	1	5	

Red: strong association with DRESS syndrome (≥ 4 points); yellow: moderate association with DRESS syndrome (2-3 points); green: weak association with DRESS syndrome (0-1 points).

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