

Supplementary Material:

5 Supplementary Tables and 10 Supplementary References

EDITORIAL

Data from the World Health Organization's pharmacovigilance database supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions

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Supplementary Table S1. First two findings: association between clozapine and pneumonia compared with other antipsychotics

STUDIES	Pneumonia		Statistical analyses	Comment
	Clozapine	Controls		
Clozapine may be associated with a greater number of pneumonia cases than other antipsychotics				
TAIWAN REGISTRY				
Kuo et al. ^{S1}	19% (336/1739)	7% schizophrenia (510/6949)	RR=3.18 (CI 2.62-3.86)	2000 to 2008
Yang et al. ^{S2}	8% (45/571)	2% bipolar (51/2277)	RR=2.59 (CI 1.46-4.63)	1998 to 2006
		10% OLA (59/571)	RR=2.97 (CI 1.90-4.66) ^a	
Hung et al. ^{S3}	20% recurrent (96/487)	16% single episode (226/1438)	RR=1.40 (CI 1.05-1.88)	For recurrent pneumonia May overlap with Kuo et al ^{S1}
Kuo et al. ^{S4}	Second rank predictor		Machine learning	185 schizophrenia inpatients
Wu et al. ^{S5}	2.98 cases per 100 person-year	1.12 cases schizophrenia per 100 person-year		1998 to 2012 May overlap with Kuo et al ^{S1}
25-MONTH RETROSPECTIVE STUDY IN US COUNTY HOSPITAL				
Stoecker et al. ^{S6}	34% (54/155)	12% (18/155) general population 14% (22/155) RIS	OR=4.07 (CI 2.25-7.36) OR=1.26 (CI 0.65-2.45;p=0.50) ^a	
VIGIBASE (>20,000,000 ADRs collected since 1968)				
de Leon et al. ⁴	4865	393 RIS 622 QUE 493 OLA	>1195 expected ^b (p<.001) ^c < 845 expected ^b < 650 expected ^b < 529 expected ^b	pneumonia on April 8, 2019
Clozapine may be associated with greater mortality during pneumonia than other antipsychotics				
PNEUMONIA DEATHS IN BRITISH STUDY FOCUSED ON DRUG DISCONTINUATION				
Taylor et al. ^{S7}	5 (1% of 529)	0 (in 250) LAI RIS		
PNEUMONIA FATAL OUTCOMES IN VIGIBASE (>140,000 clozapine ADRs collected since 1968)				
de Leon et al. ⁴	1,577 (32% of 4,865)	141 (36% of 393) RIS 105 (17% of 622) QUE 147 (30% of 493) OLA		pneumonia on April 8, 2019
This editorial	2,077 (30% of 6,983)	181 (36% of 506) RIS 189 (22% of 848) QUE 221 (32% of 685) OLA		broad pneumonia ^d on July 17, 2019

ADRs, adverse drug reactions; CI, 95% confidence interval; LAI: long-acting injections; OLA, olanzapine; OR, odds ratio; QUE, quetiapine; RR, risk ratio; RIS, risperidone; US, United States.

^aCompared to controls.

^bExpected if the antipsychotic had followed the general reporting in the database with 0.9% of the reports relating to pneumonia.

^cA standard statistical analysis for this data combining statistical shrinkage and Bayesian confidence intervals for the observed-to-expected ratio indicates a robust statistical association where the limits of the two-sided 95% confidence interval are [4.0,4.2] with a point estimate of 4.1 ($p < 0.001$). Moreover, such association is observed in separate analyses for all adult age groups and across the Americas, Asia, Europe and Oceania, reducing the likelihood of being due to report artifacts or case duplication.

^dBy adding pneumonia, lower respiratory infection and aspiration.

Supplementary Table S2. Third finding: pneumonia may be an important cause of death in clozapine patients

Author	Database	Deaths	
		Pneumonia/total	Other causes/total
Walker et al. ^{S8}	1991-1993 US clozapine	12 ^a /396	24/396 suicide 18/396 pulmonary embolism
Rohde et al. ^{S9}	Danish registry first 2 m 3,262 initiations	7/26 ^b	3/26 stroke
Ruan & de Leon ^{S10}	KY MH mortality ^c Inpatients (2002-18) Outpatients (2008-18)	1/700	1/700 myocarditis
		1/500	no other deaths
This editorial	Vigibase (1968 to 07/15/19) >140,000 clozapine ADRs	2,077 broad pneumonia	1,449 sudden death & cardiac arrest 550 broad agranulocytosis

ADRs, adverse drug reactions; m: month; KY MH: Kentucky mental health; US, United States.

^a11 deaths from pneumonia and 1 death from pneumonitis and aspiration.

^b2.1 deaths/1000 patients within 2 months of clozapine initiation.

^cKY state MH facilities (inpatients) and an assisted living program for people with intellectual disabilities (outpatients).

Supplementary Table S3. Fatal outcomes of ADRs reported to VigiBase which are likely to be associated with clozapine.

ADRs	Fatal Outcomes	Relative Lethality ^a	Reports	IC ₀₂₅ ^b
>100 FATAL OUTCOMES IN ORDER; LIKELY^c TO BE ASSOCIATED WITH CLOZAPINE				
Pneumonia	1,654	33%	4,951	1.9
Cardiac arrest	849	84%	1,014	1.1
Sudden death	619	100%	619	3.1
Seizure	283	6%	4,518	1.8
Lower respiratory tract infection	281	14%	1,974	3.1
Constipation	280	11%	2,539	0.9
Cardiac failure	271	41%	659	1.0
Aspiration	256	69%	373	3.0
Agranulocytosis	213	4%	4,798	4.4
Choking	191	66%	290	1.8
Arrhythmia	188	40%	469	0.5
Myocarditis	170	6%	3,048	5.9
Hypotension	166	8%	2,212	0.5
WBC decrease	147	4%	6,898	3.7
Neutropenia	142	1%	10,895	3.7
Leukopenia	141	1%	10,549	4.0
Tachycardia	135	2%	6,518	2.8
Cardiomyopathy	131	12%	1,132	3.7
Syncope	116	11%	1,041	0.2
OTHER OVERLAPPING^d ADRS ASSOCIATED WITH FATAL OUTCOMES				
Neutrophil count decrease	90	1%	8,998	5.1
Megacolon	56	51%	109	3.8
Paralytic ileus	51	16%	323	3.5
Granulocytopenia	46	1%	5,741	5.4
Orthostatic hypotension	32	3%	1,090	2.8
Generalized tonic-clonic seizures	27	1%	1,809	3.0

ADRs: adverse drug reactions; IC: information component; IC₀₂₅: lower 97.5% confidence intervals of the IC; WBC: white blood cell count.

^aRelative lethality = fatal outcomes/reports.

^bA Bayesian confidence propagation neural network provides a statistical indicator called IC, which is used to filter out combinations of particular drugs and ADRs that are present in the database more frequently than expected, according to all reports for the particular drug and ADRs, and the total number of reports in the database. An IC of 0 results from drug-ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the data set. Positive values represent combinations reported more frequently and negative values more infrequently than expected. The 97.5% confidence intervals of the ICs are calculated. An IC₀₂₅>0 indicates that the lowest value of the 97.5% confidence interval of the IC is higher than expected, based on the background.

^cIn the 5,352 categories of ADRs used for the 144,020 clozapine reports, another 16 ADRs had >100 fatal outcomes; a list is available from the first author. We consider that these 16 ADRs are not likely to be associated with clozapine, since there is no clear pharmacological mechanism and many of them have low IC₀₂₅. Two examples are: myocardial infarct with 1,135 fatal outcomes (69% of 1,638 reports; IC₀₂₅=0.6) and cerebrovascular accident with 174 fatal outcomes (35% of 495 reports; IC₀₂₅=-0.7).

^dThese categories overlap with those of the upper panel and ignoring them may contribute to fewer fatal outcomes for that clozapine ADR.

Supplementary Table S4. Pneumonia cases and sudden cardiac events reported to VigiBase and associated with clozapine and 3 antipsychotics

ADRs	Clozapine	Risperidone	Quetiapine	Olanzapine
Grouped ADRs				
	Fatal outcomes/cases (%)	Fatal outcomes/cases (%)	Fatal outcomes/cases (%)	Fatal outcomes/cases (%)
Broad pneumonia ^a	2,077/6,983 (30%)	181/506 (36%)	189/848 (22%)	221/685 (32%)
Sudden deaths and cardiac arrests ^b	1,449/1,614 (90%)	486/591 (82%)	871/1,014 (86%)	609/726 (84%)
Broad arrhythmia ^c	319/6,927 (5%)	91/1,466 (6%)	131/1,515 (9%)	125/1,216(10%)
ADRs included in above groups				
Pneumonia	1,654/4,951 (33%)	153/435 (35%)	124/692 (18%)	165/572 (29%)
Lower respiratory tract infection	281/1,974 (14%)	3/21 (14%)	1/35 (3%)	4/27 (15%)
Aspiration	256/373 (69%)	29/59 (49%)	67/134 (50%)	56/100 (56%)
Cardiac arrest	849/1,014 (84%)	306/411 (74%)	769/912 (84%)	404/521 (76%)
Sudden deaths	619/619 (100%)	186/186 (100%)	105/105 (100%)	212/212 (100%)
Arrhythmia	188/469 (40%)	56/217 (26%)	72/274 (26%)	78/222 (35%)
Tachycardia	135/6,518 (2%)	37/1,262 (3%)	64/1,258 (5%)	47/1,008 (5%)

ADRs: adverse drug reactions.

^aBy adding pneumonia, lower respiratory infection and aspiration.

^bBy adding cardiac arrest and sudden death.

^cBy adding tachycardia and arrhythmias.

Supplementary Table S5. Total ADR reports of clozapine, risperidone, quetiapine and olanzapine in VigiBase

ADRs	Clozapine	Risperidone	Quetiapine	Olanzapine
	N	N	N	N
Total number of reports	144,020	100,283	80,503	63,827
Number of different ADRs	5,352	4,417	5,479	4,766

ADR: adverse drug reaction.

Supplementary References

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