

Data supplement for Taipale et al., Safety of Antipsychotic Polypharmacy Versus Monotherapy in a Nationwide Cohort of 61,889 Patients With Schizophrenia. *Am J Psychiatry* (doi: 10.1176/appi.ajp.20220446)

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TABLE S1. Defined daily doses (DDDs) determined by World Health Organization
(https://www.whooc.no/ddd/definition_and_general_considera/)

	DDD value as mg/day
Second generation orals	
Aripiprazole oral	15.0
Clozapine oral	300
Olanzapine oral	10.0
Quetiapine oral	400
Risperidone oral	5.0
Sertindole oral	16.0
Ziprasidone oral	80.0
Second generation LAIs	
Olanzapine LAI	10.0
Paliperidone LAI	2.5
Risperidone LAI	2.7
Aripiprazole LAI	13.3

Paliperidone LAI refers to once-monthly injection.

TABLE S2. Risk of outcomes associated with polypharmacy when compared with the same dose monotherapy use (reference) when clozapine has been excluded from both categories. Adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs) and p-values from within-individual model. DDD: Defined Daily Dose.

Dose group	aHR (95% CI)	p-value
Non-psychiatric hospitalization		
<0.4	1.03 (0.98-1.09)	0.2387
0.4-<0.6	0.93 (0.88-0.97)	0.0027
0.6-<0.9	0.89 (0.86-0.93)	<.0001
0.9-<1.1	0.93 (0.88-0.98)	0.0032
1.1-<1.4	0.84 (0.80-0.88)	<.0001
1.4-<1.6	0.87 (0.82-0.93)	<.0001
≥1.6	0.82 (0.79-0.85)	<.0001
Cardiovascular hospitalization		
<0.4	0.95 (0.80-1.14)	0.607
0.4-<0.6	0.95 (0.80-1.13)	0.569
0.6-<0.9	0.91 (0.79-1.06)	0.221
0.9-<1.1	0.94 (0.78-1.13)	0.5007
1.1-<1.4	0.81 (0.68-0.97)	0.0232
1.4-<1.6	0.88 (0.69-1.12)	0.2977
≥1.6	0.84 (0.74-0.96)	0.0105

TABLE S3. Risk of non-psychiatric and cardiovascular hospitalization associated with polypharmacy when compared with the same dose monotherapy use, when first 30 days are excluded from each exposure. Adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs) and p-values from within-individual model. DDD: Defined Daily Dose.

Dose category (DDDs/day)	Monotherapy		Polypharmacy		aHR (95% CI)	p-value
	Person-years	Events	Person-years	Events		
Non-psychiatric hospitalization						
<0.4	63766	19822	7501	2533	1.11 (1.04-1.18)	0.0013
0.4-<0.6	38197	8749	12185	3291	1.02 (0.96-1.08)	0.6198
0.6-<0.9	50925	10220	21646	5528	0.98 (0.93-1.02)	0.2924
0.9-<1.1	35900	6456	14246	3368	1.00 (0.94-1.06)	0.8662
1.1-<1.4	29272	5197	22343	5117	0.93 (0.89-0.99)	0.0141
1.4-<1.6	13438	2426	13254	2910	0.93 (0.87-1.01)	0.068
≥1.6	46277	9139	119538	28077	0.94 (0.90-0.97)	0.0007
Cardiovascular hospitalization						
<0.4	63766	2866	7501	344	1.01 (0.83-1.24)	0.8983
0.4-<0.6	38197	1155	12185	437	1.09 (0.89-1.33)	0.4011
0.6-<0.9	50925	1113	21646	601	1.03 (0.86-1.23)	0.7442
0.9-<1.1	35900	636	14246	390	1.03 (0.83-1.28)	0.8005
1.1-<1.4	29272	490	22343	490	0.97 (0.78-1.20)	0.7529
1.4-<1.6	13438	228	13254	310	1.06 (0.78-1.45)	0.6925
≥1.6	46277	824	119538	2313	0.96 (0.81-1.13)	0.6084

TABLE S4. Risk of non-psychiatric and cardiovascular hospitalization associated with monotherapy when compared with non-use of antipsychotics in different dose categories, stratified by the use of antipsychotic polypharmacy during the follow-up. Adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs) and p-values from within-individual model. DDD: Defined Daily Dose.

	Ever polypharmacy N=42042		Never polypharmacy N=19487		Ever polypharmacy		Never polypharmacy	
	Events	Person-years	Events	Person-years	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Non-psychiatric hospitalization								
<0.4	16274	51786	8188	18718	1.08 (1.05-1.12)	<0.0001	1.03 (0.98-1.08)	0.2866
0.4-<0.6	8309	33194	3162	10849	1.06 (1.02-1.10)	0.0068	1.00 (0.94-1.07)	0.9440
0.6-<0.9	10503	46338	3233	13822	1.09 (1.05-1.13)	<0.0001	1.08 (1.00-1.15)	0.0386
0.9-<1.1	6885	32884	1991	10416	1.05 (1.01-1.10)	0.0155	0.99 (0.92-1.08)	0.8702
1.1-<1.4	6376	29793	1671	9259	1.16 (1.11-1.21)	<0.0001	1.14 (1.04-1.24)	0.0039
1.4-<1.6	3414	15059	728	4330	1.18 (1.12-1.25)	<0.0001	1.11 (0.98-1.25)	0.0909
≥1.6	12867	51437	2801	12769	1.38 (1.33-1.44)	<0.0001	1.38 (1.27-1.50)	<0.0001
Cardiovascular hospitalization								
<0.4	2118	48867	1437	22123	1.08 (0.97-1.21)	0.1733	1.03 (0.90-1.17)	0.6816
0.4-<0.6	1024	32517	469	11693	1.03 (0.90-1.18)	0.7052	0.98 (0.81-1.19)	0.8188
0.6-<0.9	1104	45856	416	14512	0.98 (0.86-1.13)	0.8140	1.02 (0.83-1.26)	0.8459
0.9-<1.1	672	32682	205	10755	1.10 (0.94-1.29)	0.2229	0.88 (0.65-1.17)	0.3735
1.1-<1.4	616	29682	135	9467	1.12 (0.95-1.32)	0.1839	0.84 (0.60-1.18)	0.3248
1.4-<1.6	300	15022	67	4412	1.29 (1.03-1.62)	0.0264	0.61 (0.38-0.99)	0.0460
≥1.6	1161	51274	254	13119	1.50 (1.29-1.74)	<0.0001	1.55 (1.15-2.11)	0.0044

TABLE S5. The risk of outcomes associated with the highest doses of specific monotherapies when compared with polypharmacy of the same antipsychotics used with the highest dose category (≥ 1.6 DDD/day) in within-individual model. The reference value is each two-drug combination and monotherapies of those two drugs are compared with that. Five most common antipsychotics were chosen for comparisons. CLZ=clozapine, OLA=olanzapine, QUE=quetiapine, RIS=risperidone, ARI=aripiprazole. Cardiovascular (CV) hospitalization associated with RIS-ARI could not be analyzed due to lack of events (sparsity of data). The results of combinations differing statistically significantly from both of its monotherapy components in the same patients are indicated with bold. The only monotherapy showing nominally statistically significantly lower risk of hospitalization was olanzapine when compared with clozapine-olanzapine polypharmacy for non-psychiatric hospitalization (level of significance $p < 0.05$).

	Non-psychiatric hospitalization HR (95% CI)	CV hospitalization HR (95% CI)
CLZ-OLA ≥ 1.6 DDDs/day as reference		
CLZ ≥ 1.6 DDDs/day monotherapy	0.88 (0.77-1.01)	2.26 (0.88-5.81)
OLA ≥ 1.6 DDDs/day monotherapy	0.85 (0.74-0.96)	1.83 (0.73-4.55)
CLZ-QUE ≥ 1.6 DDDs/day as reference		
CLZ ≥ 1.6 DDDs/day monotherapy	1.16 (1.00-1.34)	0.84 (0.31-2.27)
QUE ≥ 1.6 DDDs/day monotherapy	1.14 (0.97-1.34)	0.78 (0.28-2.19)
CLZ-RIS ≥ 1.6 DDDs/day as reference		
CLZ ≥ 1.6 DDDs/day monotherapy	0.92 (0.78-1.10)	2.54 (0.81-7.95)
RIS ≥ 1.6 DDDs/day monotherapy	1.14 (0.91-1.42)	2.96 (0.88-9.97)
CLZ-ARI ≥ 1.6 DDDs/day as reference		
CLZ ≥ 1.6 DDDs/day monotherapy	1.24 (1.11-1.38)	1.73 (0.82-3.64)
ARI ≥ 1.6 DDDs/day monotherapy	1.35 (1.10-1.65)	1.50 (0.52-4.37)
OLA-QUE ≥ 1.6 DDDs/day as reference		
OLA ≥ 1.6 DDDs/day monotherapy	1.06 (0.97-1.16)	2.33 (1.35-4.01)
QUE ≥ 1.6 DDDs/day monotherapy	1.10 (0.98-1.23)	2.72 (1.41-5.24)
OLA-RIS ≥ 1.6 DDDs/day as reference		
OLA ≥ 1.6 DDDs/day monotherapy	1.15 (1.02-1.31)	1.20 (0.67-2.16)
RIS ≥ 1.6 DDDs/day monotherapy	1.48 (1.22-1.79)	1.74 (0.81-3.74)
OLA-ARI ≥ 1.6 DDDs/day as reference		
OLA ≥ 1.6 DDDs/day monotherapy	1.08 (0.94-1.23)	0.99 (0.51-1.91)
ARI ≥ 1.6 DDDs/day monotherapy	1.23 (0.99-1.52)	1.07 (0.38-3.02)
RIS-QUE ≥ 1.6 DDDs/day as reference		
RIS ≥ 1.6 DDDs/day monotherapy	1.41 (1.15-1.73)	1.96 (0.91-4.25)
QUE ≥ 1.6 DDDs/day monotherapy	1.13 (0.97-1.33)	1.59 (0.78-3.23)
ARI-QUE ≥ 1.6 DDDs/day as reference		
ARI ≥ 1.6 DDDs/day monotherapy	1.23 (0.99-1.53)	1.02 (0.36-2.87)
QUE ≥ 1.6 DDDs/day monotherapy	1.11 (0.95-1.30)	1.10 (0.52-2.33)
RIS-ARI ≥ 1.6 DDDs/day as reference		
RIS ≥ 1.6 DDDs/day monotherapy	1.37 (0.93-2.04)	NA
ARI ≥ 1.6 DDDs/day monotherapy	1.22 (0.81-1.82)	NA

TABLE S6. Risk of psychiatric hospitalization associated with specific monotherapy and polypharmacy dose categories in comparison with no antipsychotic use, and head-to-head comparison of specific polypharmacy dose categories with the corresponding monotherapy dose categories in within-individual models. Adjusted Hazard Ratios (HRs) with 95% confidence intervals (CIs). DDD: Defined Daily Dose.

Dose group (DDDs/ day)	Users, N	Person-years	Events	Compared with non-use of antipsychotics	Head-to-head comparison of polypharmacy dose categories with the corresponding monotherapy dose categories
				Adjusted HR (95% CI)	Adjusted HR (95% CI)
Polypharmacy					
<0.4	5530	8275	1085	0.57 (0.52-0.62)	0.87 (0.80-0.95)
0.4-<0.6	9871	13641	2112	0.48 (0.46-0.51)	0.88 (0.83-0.94)
0.6-<0.9	17336	24785	4830	0.47 (0.45-0.49)	0.92 (0.88-0.96)
0.9-<1.1	17046	17198	4018	0.47 (0.45-0.49)	1.00 (0.96-1.05)
1.1-<1.4	22426	27291	7061	0.46 (0.45-0.48)	0.90 (0.87-0.94)
1.4-<1.6	19577	17184	4881	0.47 (0.45-0.49)	0.86 (0.82-0.90)
≥1.6	32556	137636	58214	0.57 (0.56-0.58)	0.86 (0.84-0.88)
Monotherapy					
<0.4	28439	70653	11591	0.65 (0.64-0.67)	
0.4-<0.6	25739	43919	7744	0.55 (0.53-0.57)	
0.6-<0.9	30652	59716	12381	0.51 (0.49-0.52)	
0.9-<1.1	26407	42888	8250	0.47 (0.45-0.48)	
1.1-<1.4	26508	38454	10030	0.51 (0.50-0.53)	
1.4-<1.6	19950	19060	5415	0.55 (0.53-0.57)	
≥1.6	28702	62960	23145	0.66 (0.65-0.68)	

FIGURE S1. Study design and time-varying exposure

