



Supplementary Material

Article Title: Antipsychotic Treatment and the Risk of Hip Fracture in Subjects With Schizophrenia: A 10-Year Population-Based Case-Control Study

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Supplementary eTable 1. Receptor binding affinity (pK_i)* for antipsychotic drugs

Drug name	5HT _{2A}	D ₂	α ₁	H ₁
First-generation antipsychotics				
Chlorpromazine	7.96	8.29	8.59	8.51
Clothiapine	8.46	-	-	-
Flupentixol	7.06	8.82	-	9.07
Fluphenazine	7.42	9.27	8.20	7.85
Haloperidol	6.81	8.92	7.77	5.77
Perphenazine	8.25	9.04	8.00	8.10
Thioridazine	7.56	7.98	8.30	7.78
Trifluoperazine	7.13	8.89	7.62	7.20
Second-generation antipsychotics				
Amisulpride	5.08	8.89	5.00	5.00
Clozapine	7.80	7.27	8.17	8.95
Olanzapine	8.62	7.28	7.36	8.66
Quetiapine	6.04	6.39	8.09	8.16
Risperidone	9.23	8.24	8.57	7.70
Sulpiride	5.00	7.84	5.00	5.00
Zotepine	8.57	7.60	8.14	8.49

Note:

Abbreviations: 5HT_{2A}=serotonin 5-HT_{2A} receptor; D₂=dopamine D₂ receptor; α₁ adrenergic receptor; H₁=H₁ histaminergic receptor.

* A minimal (pK_i) value of 5.0 was used for low binding affinity.

Supplementary eTable 2. Demographic and clinical characteristics of the FGAs, SGAs and combination drug users.

	FGAs		SGAs		combination		<i>P-value</i> ^a
	(n=375)		(n=1,415)		(n=436)		
	n	%	n	%	n	%	
Age (mean ± SD)	55.22±15.55		58.38±16.75		52.28±15.90		NP ^b
Sex							
Male	219	58.40	750	53.00	229	52.52	NP ^b
Female	156	41.60	665	47.00	207	47.48	
No. of ambulatory visits							
0	0	0	0	0	0	0	0.02
1-10	47	12.53	139	9.82	35	8.03	
11-20	94	25.07	326	23.04	81	18.58	
≥ 21	234	62.40	950	67.14	320	73.39	
No. of inpatient visits							
0	225	60.00	819	57.88	186	42.66	<0.0001
1	77	20.53	289	20.42	126	28.9	
≥ 2	73	19.47	307	21.70	124	28.44	
Medical comorbidity							
Anemia	16	4.27	87	6.15	19	4.36	0.19
Coronary Heart Disease	1	0.27	10	0.71	3	0.69	0.62
Hypertension	100	26.67	370	26.15	109	25.00	0.85
Cerebrovascular disease	17	4.53	128	9.05	42	9.63	0.02
Chronic Pulmonary Disease	47	12.53	206	14.56	62	14.22	0.61
Diabetes mellitus	57	15.20	209	14.77	59	13.53	0.76
Malignant neoplasm	7	1.87	37	2.61	9	2.06	0.62
Peripheral Vascular Disease	7	1.87	21	1.48	5	1.15	0.70
Parkinson's disease	16	4.27	117	8.27	36	8.26	0.03
Rheumatoid arthritis	2	0.53	9	0.64	2	0.46	0.90
Renal failure	5	1.33	20	1.41	4	0.92	0.73
Psychiatry comorbidity							
Sleep disorder	92	24.53	287	20.28	134	30.73	<0.0001
Alcohol-related disorder	23	6.13	36	2.54	25	5.37	0.0003
Substance use disorder	12	3.20	22	1.55	21	4.82	0.0004
Dementia	28	7.47	214	15.12	34	7.80	0.87
Medication use							
Antidepressants	98	26.13	399	28.20	178	40.83	<0.0001
Anticonvulsants	75	20.00	289	20.42	125	28.67	0.0008
Anxiolytics	191	50.93	768	54.28	291	66.74	<0.0001
Benzodiazepines	196	52.27	737	52.08	280	64.22	<0.0001
Oral glucocorticosteroids	47	12.53	153	10.81	58	13.30	0.30
Hormone replacement therapy	13	3.47	61	4.31	24	5.50	0.36

Note:

Abbreviations: SD=standard deviation.

^a *P* values were obtained from univariate analysis; Student's *t* test was used for continuous variables and chi-square test was used for discrete variables.

^b NP=not-provided since the controls were matched to cases on age and sex.

Supplementary eTable 3. Association of the use of each antipsychotic drug* with risk of hip fracture.

	Cases (n=605)		Controls (n=2,828)		Model 1 ^{#,a}	95% CI	Model 2 [#]	95% CI	Model 3 [#]	95%CI
	n	%	n	%						
Any use of FGAs										
PROCHLORPERAZINE ^b										
Current users	3	0.5	14	0.5	1.06	(0.30, 3.69)	0.78	(0.22, 2.78)	0.77	(0.22, 2.75)
Past users	9	1.49	32	1.13	1.27	(0.60, 2.73)	0.80	(0.36, 1.80)	0.78	(0.35, 1.75)
HALOPERIDOL ^b										
Current users	51	8.43	144	5.09	1.88	(1.34, 2.64)	1.82	(1.28, 2.58)	1.84	(1.30, 2.61)
Past users	47	7.77	134	4.74	1.91	(1.34, 2.72)	1.47	(1.02, 2.13)	1.49	(1.03, 2.16)
CHLORPROMAZINE ^b										
Current users	10	1.65	43	1.52	1.18	(0.59, 2.37)	1.03	(0.50, 2.10)	0.99	(0.49, 2.01)
Past users	12	1.98	29	1.03	2.08	(1.06, 4.11)	1.54	(0.75, 3.13)	1.54	(0.76, 3.13)
TRIFLUOPERAZINE ^b										
Current users	7	1.16	17	0.6	2.01	(0.83, 4.86)	1.90	(0.78, 4.64)	1.96	(0.81, 4.79)
Past users	3	0.5	10	0.35	1.00	(0.22, 4.56)	1.09	(0.24, 5.04)	1.09	(0.23, 5.03)
THIORIDAZINE ^b										
Current users	3	0.5	18	0.64	0.83	(0.25, 2.83)	0.78	(0.23, 2.72)	0.80	(0.23, 2.77)
Past users	8	1.32	14	0.5	2.87	(1.20, 6.87)	2.56	(1.04, 6.31)	2.61	(1.06, 6.42)
FLUPENTIXOL ^b										
Current users	32	5.29	104	3.68	1.51	(0.99, 2.29)	1.45	(0.94, 2.22)	1.43	(0.93, 2.20)
Past users	25	4.13	78	2.76	1.57	(0.99, 2.49)	1.19	(0.73, 1.93)	1.18	(0.73, 1.91)
CLOTHIAPINE ^b										
Current users	12	1.98	25	0.88	2.47	(1.23, 4.97)	2.22	(1.08, 4.56)	2.27	(1.11, 4.65)
Past users	4	0.66	15	0.53	1.39	(0.46, 4.18)	1.01	(0.33, 3.11)	0.99	(0.32, 3.04)

Any use of SGAs										
RISPERIDONE^b										
Current users	81	13.39	343	12.13	1.18	(0.91, 1.54)	1.15	(0.87, 1.51)	1.16	(0.88, 1.52)
Past users	57	9.42	200	7.07	1.40	(1.01, 1.93)	1.22	(0.87, 1.70)	1.21	(0.87, 1.69)
QUETIAPINE^b										
Current users	55	9.09	177	6.26	1.38	(0.99, 1.92)	1.15	(0.81, 1.63)	1.14	(0.81, 1.62)
Past users	25	4.13	109	3.85	1.11	(0.71, 1.74)	0.80	(0.50, 1.28)	0.81	(0.51, 1.29)
OLANZAPINE^b										
Current users	29	4.79	106	3.75	1.38	(0.90, 2.12)	1.24	(0.80, 1.91)	1.24	(0.81, 1.92)
Past users	22	3.64	70	2.48	1.53	(0.93, 2.53)	1.20	(0.72, 2.01)	1.19	(0.71, 1.99)
ZOTEPINE^b										
Current users	13	2.15	55	1.94	1.10	(0.58, 2.09)	0.94	(0.49, 1.82)	0.94	(0.48, 1.81)
Past users	13	2.15	36	1.27	1.66	(0.86, 3.19)	1.29	(0.65, 2.56)	1.31	(0.67, 2.59)
AMISULPRIDE^b										
Current users	13	2.15	53	1.87	1.23	(0.66, 2.28)	1.06	(0.56, 1.99)	1.04	(0.55, 1.96)
Past users	10	1.65	51	1.8	0.98	(0.49, 1.94)	0.88	(0.44, 1.78)	0.88	(0.44, 1.76)
SULPIRIDE^b										
Current users	60	9.92	223	7.89	1.43	(1.06, 1.94)	1.30	(0.95, 1.79)	1.31	(0.96, 1.79)
Past users	58	9.59	149	5.27	2.06	(1.48, 2.86)	1.59	(1.13, 2.25)	1.60	(1.14, 2.26)
CLOZAPINE^b										
Current users	12	1.98	91	3.22	0.59	(0.31, 1.12)	0.59	(0.31, 1.12)	0.60	(0.31, 1.13)
Past users	9	1.49	35	1.24	1.10	(0.51, 2.39)	0.98	(0.44, 2.17)	0.99	(0.45, 2.19)
ARIPIPRAZOLE^b										

Current users	9	1.49	43	1.52	NA	NA	NA
Past users	1	0.17	32	1.13			

Note:

[#] Model 1: crude analysis; Model 2: adjusted analysis including all covariates listed in Table 1; Model 3: adjusted analysis including the covariates listed in Table 1 and $p < 0.15$ after stepwise selection (anemia, hypertension, cerebrovascular disease, chronic pulmonary disease, Parkinson's disease, renal failure, sleep disorder, alcohol-related disorder, dementia, antidepressants, anticonvulsants, anxiolytics, benzodiazepines, hormone replacement therapy, ambulatory visits and inpatient visits).

* Antipsychotic use is defined as at least one day of antipsychotic drug supply within the 6 months prior to the index date.

^a Significant results ($p < 0.05$) are in bold.

^b Subjects without antipsychotic use were used as the reference group.