1   Study title:

2   Mortality risk associated with haloperidol use compared with other antipsychotics: an 11-year population-based

3   propensity-score-matched cohort study

4

5   Running heading:

6   Risk of mortality associated with haloperidol compared with other antipsychotics

7

8   Authors: Kim SJ Lao[1, 2], PhD; Angel YS Wong[3], PhD; Ian CK Wong[1, 4], PhD; Frank MC Besag[4, 5, 6], FRCP; WC

9   Chang[7, 8], FHKCPsych; Edwin HM Lee[7], MSc; Eric YH Chen[7, 8], MD; Joseph E Blais[1], BScPharm; Esther W Chan[1],

10   PhD

11

12   Affiliations: [1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The

13   University of Hong Kong, Hong Kong SAR, China; [2]Global Medical Affairs, Merck Research Laboratories, MSD

14   China; [3]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine,

15   London, UK; [4]Research Department of Practice and Policy, UCL School of Pharmacy, London, UK; [5]East London

16   NHS Foundation Trust, Bedfordshire, UK; [6]Institute of Psychiatry, Psychology and Neuroscience, London, UK;

17   [7]Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR,

18   China; [8]State Key Laboratory of Brain & Cognitive Sciences, The University of Hong Kong, Hong Kong SAR,

19   China.

20

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23   Correspondence to:

24   Dr Esther W Chan

25   Associate Professor

26   Research Lead, Centre for Safe Medication Practice and Research

27   Department of Pharmacology and Pharmacy

28   Office 02-08, 2/F Laboratory Block, 21 Sassoon Road, Pokfulam

29   Li Ka Shing Faculty of Medicine

30   The University of Hong Kong

31   Hong Kong SAR, China

32   Email: ewchan@hku.hk

33   Centre: +852 2831 5110

34   Office: +852 3917 9029

35

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36   Online-Only Supplements

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BNF	Description
Antipsychotic	
4.2.1	Antipsychotic drugs
4.2.2	Antipsychotic depot injections
Antidepressant	
4.3.1	Tricyclic and related antidepressant drugs
4.3.2	Monoamine-oxidase inhibitors
4.3.3	Selective serotonin re-uptake inhibitors
4.3.4	Other antidepressant drugs
Hypnotic and anxiolytics	
4.1.1	Hypnotics
4.1.2	Anxiolytics
4.1.3	Barbiturates
Antiepileptic	
4.8.1	Control of the epilepsies
4.8.2	Drugs used in status epilepticus
4.8.3	Febrile convulsions
Anti-manic	
4.2.3	Drugs used for mania and hypomania
Antidiabetic	
6.1.1	Insulins
6.1.2	Antidiabetic drugs
6.1.3	Diabetic ketoacidosis
6.1.4	Treatment of hypoglycemia
6.1.5	Treatment of diabetic nephropathy and neuropathy
6.1.6	Diagnostic and monitoring devices for diabetes mellitus
Drug used in hypertension and heart failure	
2.5.1	Vasodilator antihypertensive drugs
2.5.2	Centrally acting antihypertensive drugs
2.5.3	Adrenergic neurone blocking drugs
2.5.4	Alpha-adrenoceptor blocking drugs
2.5.5	Drugs affecting the renin-angiotensin system

59 **eTable 1.** *British National Formulary* **(BNF) Codes Used in This Study**

60

BNF	Description
Antiplatelet	
2.9	Antiplatelet drugs
Calcium channel blocker	
2.6.2	Calcium channel blockers
Diuretic	
2.2.1	Thiazides and related diuretics
2.2.2	Loop diuretics
2.2.3	Potassium-sparing diuretics and aldosterone antagonists
2.2.4	Potassium-sparing diuretics with other diuretics
2.2.5	Osmotic diuretics
2.2.6	Mercurial diuretics
2.2.7	Carbonic anhydrase inhibitors
2.2.8	Diuretics with potassium
Beta blocker	
2.4	Beta-adrenoceptor blocking drugs
Antiarrhythmic	
2.3.2	Drugs for arrhythmias
Digoxin	
2.1.1	Cardiac glycosides
Nitrates	
2.6.1	Nitrates
Anticoagulant	
2.8.1	Parenteral anticoagulants
2.8.2	Oral anticoagulants
2.8.3	Protamine sulfate
2.8.4	Idarucizumab
Peripheral vasodilator	
2.6.4	Peripheral vasodilators and related drugs
Lipid regulating drugs	
2.12	Lipid regulating drugs

61   **eTable 1.** *British National Formulary* (**BNF**) **Codes Used in This Study (continued)**

62

BNF	Description
Oral corticosteroid	
3.2	Corticosteroids
6.3	Corticosteroids
Non-steroidal anti-inflammatory drugs	
10.1.1	Non-steroidal anti-inflammatory drugs
Proton pump inhibitors	
1.3.5	Proton pump inhibitors
Histamine-2 receptor blocker	
1.3.1	H2-receptor antagonists
Antibacterial	
5.1.1	Penicillins
5.1.2	Cephalosporins, carbapenems, and other beta-lactams
5.1.3	Tetracyclines
5.1.4	Aminoglycosides
5.1.5	Macrolides
5.1.6	Clindamycin
5.1.7	Some other antibacterials
5.1.8	Sulfonamides and trimethoprim
5.1.9	Antituberculosis drugs
5.1.10	Antileprotic drugs
5.1.11	Metronidazole and tinidazole
5.1.12	Quinolones
5.1.13	Urinary-tract infections
Antifungal	
5.2.1	Triazole antifungals
5.2.2	Imidazole antifungals
5.2.3	Polyene antifungals
5.2.4	Echinocandin antifungals
5.2.5	Other antifungals
Antiviral	
5.3.1	HIV infection
5.3.2	Herpesvirus infections
5.3.3	Viral hepatitis
5.3.4	Influenza
5.3.5	Respiratory syncytial virus

63 **eTable 1.** *British National Formulary* **(BNF) Codes Used in This Study (continued)**

64

65

ICD-9-CM	Description
Schizophrenia	
259	Schizophrenic disorders
Bipolar disorder	
296.0	Bipolar I disorder, single manic episode
296.4	Bipolar I disorder, most recent episode (or current) manic
296.5	Bipolar I disorder, most recent episode (or current) depressed
296.6	Bipolar I disorder, most recent episode (or current) mixed
296.7	Bipolar I disorder, most recent episode (or current) unspecified
296.8	Other and unspecified bipolar disorders
Other psychoses	
296.1	Manic disorder recurrent episode
296.9	Other and unspecified episodic mood disorder
298	Other nonorganic psychoses
299	Pervasive developmental disorders
Major depressive disorder	
296.2	Major depressive disorder single episode
296.3	Major depressive disorder recurrent episode
Dementia	
290	Dementias
Anxiety disorder	
300	Anxiety, dissociative and somatoform disorders
Delusional disorder	
297	Delusional disorders
Personality disorder	
301	Personality disorders
Post-traumatic stress disorder	
309.81	Posttraumatic stress disorder

66   **eTable 2.** *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) Codes

67   **Used in This Study**

68

ICD-9-CM	Description
Sleep disorder	
292.85	Drug induced sleep disorders
307.40	Nonorganic sleep disorder, unspecified
327	Organic sleep disorders
780.57	Unspecified sleep apnea
Behavioral problem	
312	Disturbance of conduct not elsewhere classified
Myocardial infarction	
410	Acute myocardial infarction
412	Old myocardial infarction
Arrhythmia	
427	Cardiac dysrhythmias
Other ischemic heart disease	
411	Other acute and subacute forms of ischemic heart disease
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
Congestive heart disease	
428	Heart failure
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
Cerebrovascular disease	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
436	Acute, but ill-defined, cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease

70 **eTable 2.** *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) **Codes**

71 **Used in the Study (continued)**

72

Version Date: 20191113

ICD-9-CM	Description
Diabetes mellitus	
250	Diabetes mellitus
Chronic kidney disease	
585	Chronic kidney disease
Hypothyroidism	
243	Congenital hypothyroidism
244	Acquired hypothyroidism
Parkinson's disease	
332	Parkinson's disease
Hepatic disease	
570	Acute and subacute necrosis of liver
571	Chronic liver disease and cirrhosis
572	Liver abscess and sequelae of chronic liver disease
573	Other disorders of liver
Chronic obstructive pulmonary disease	
490	Bronchitis, not specified as acute or chronic
491	Chronic bronchitis
492	Emphysema
494	Bronchiectasis
496	Chronic airway obstruction, not elsewhere classified
Suicide	
E950	Suicide and self-inflicted poisoning by solid or liquid substances
E951	Suicide and self-inflicted poisoning by gases in domestic use
E952	Suicide and self-inflicted poisoning by other gases and vapors
E953	Suicide and self-inflicted injury by hanging strangulation and suffocation
E954	Suicide and self-inflicted injury by submersion [drowning]
E955	Suicide and self-inflicted injury by firearms air guns and explosives
E956	Suicide and self-inflicted injury by cutting and piercing instrument
E957	Suicide and self-inflicted injuries by jumping from high place
E958	Suicide and self-inflicted injury by other and unspecified means
E959	Late effects of self-inflicted injury

73

74 **eTable 2.** *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) Codes

75 **Used in the Study (continued)**

76

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ICD-10-CM	Description
Cardiovascular system diseases	
I00-I02	Acute rheumatic fever
I05-I09	Chronic rheumatic heart diseases
I10-I16	Hypertensive diseases
I20-I25	Ischemic heart diseases
I26-I28	Pulmonary heart disease and diseases of pulmonary circulation
I30-I52	Other forms of heart disease
I60-I69	Cerebrovascular diseases
I70-I79	Diseases of arteries, arterioles and capillaries
I80-I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I95-I99	Other and unspecified disorders of the circulatory system
Pneumonia	
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Hemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism

78 **eTable 3.** *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) Codes

79 **Used in the Study**

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No. (%)	Amisulpride-haloperidol cohort			Aripiprazole-haloperidol cohort			Chlorpromazine-haloperidol cohort			Olanzapine-haloperidol cohort		
	Haloperidol	Amisulpride	SD	Haloperidol	Aripiprazole	SD	Haloperidol	Chlorpromazine	SD	Haloperidol	Olanzapine	SD
Demographic												
Male	29389 (44.9)	861 (40.3)	.092	29389 (44.9)	295 (33.9)	.226	29389 (44.9)	7084 (75.4)	.657	29389 (44.9)	734 (41.2)	.074
Age, mean (SD)	73.77 (18.26)	54.94 (22.98)	.907	73.77 (18.26)	45.41 (19.02)	1.521	73.77 (18.26)	53.76 (17.67)	1.114	73.77 (18.26)	43.05 (16.86)	1.748
Medication use												
No. of recent prescriptions, mean (SD)	82.13 (122.72)	34.75 (66.10)	.481	82.13 (122.72)	35.30 (68.46)	.471	82.13 (122.72)	56.03 (111.23)	.223	82.13 (122.72)	22.96 (55.81)	.621
Antidepressant	8850 (13.5)	627 (29.4)	.394	8850 (13.5)	482 (55.4)	.982	8850 (13.5)	2061 (21.9)	.222	8850 (13.5)	535 (30.0)	.409
Hypnotic/anxiolytic	12397 (18.9)	623 (29.2)	.242	12397 (18.9)	376 (43.2)	.544	12397 (18.9)	2313 (24.6)	.138	12397 (18.9)	558 (31.3)	.289
Antiepileptic	4549 (6.9)	168 (7.9)	.035	4549 (6.9)	167 (19.2)	.370	4549 (6.9)	1014 (10.8)	.136	4549 (6.9)	246 (13.8)	.227
Antidiabetic	14322 (21.9)	242 (11.3)	.286	14322 (21.9)	65 (7.5)	.415	14322 (21.9)	1387 (14.8)	.184	14322 (21.9)	61 (3.4)	.577
Drugs used in hypertension and heart failure	24877 (38.0)	329 (15.4)	.528	24877 (38.0)	98 (11.3)	.652	24877 (38.0)	2172 (23.1)	.327	24877 (38.0)	86 (4.8)	.883
Antiplatelet	25168 (38.4)	333 (15.6)	.532	25168 (38.4)	82 (9.4)	.723	25168 (38.4)	1743 (18.6)	.451	25168 (38.4)	81 (4.5)	.905
Calcium channel blockers	26879 (41.0)	397 (18.6)	.506	26879 (41.0)	115 (13.2)	.659	26879 (41.0)	2128 (22.7)	.402	26879 (41.0)	133 (7.5)	.851
Loop diuretics	15026 (22.9)	132 (6.2)	.489	15026 (22.9)	29 (3.3)	.606	15026 (22.9)	862 (9.2)	.382	15026 (22.9)	26 (1.5)	.695
Other diuretics	7232 (11.0)	112 (5.2)	.213	7232 (11.0)	24 (2.8)	.331	7232 (11.0)	706 (7.5)	.122	7232 (11.0)	35 (2.0)	.374
Beta blockers	19003 (29.0)	370 (17.3)	.279	19003 (29.0)	145 (16.7)	.297	19003 (29.0)	2088 (22.2)	.156	19003 (29.0)	166 (9.3)	.517
Antiarrhythmic	1759 (2.7)	19 (0.9)	.136	1759 (2.7)	9 (1.0)	.122	1759 (2.7)	129 (1.4)	.093	1759 (2.7)	4 (0.2)	.207
Digoxin	3804 (5.8)	39 (1.8)	.209	3804 (5.8)	9 (1.0)	.265	3804 (5.8)	175 (1.9)	.206	3804 (5.8)	12 (0.7)	.293
Nitrate	11261 (17.2)	151 (7.1)	.314	11261 (17.2)	30 (3.4)	.464	11261 (17.2)	795 (8.5)	.263	11261 (17.2)	38 (2.1)	.527
Anticoagulant	5751 (8.8)	51 (2.4)	.281	5751 (8.8)	18 (2.1)	.300	5751 (8.8)	618 (6.6)	.083	5751 (8.8)	14 (0.8)	.381
Peripheral vasodilator	1661 (2.5)	67 (3.1)	.036	1661 (2.5)	7 (0.8)	.135	1661 (2.5)	98 (1.0)	.113	1661 (2.5)	9 (0.5)	.166
Lipid lowering drugs	12203 (18.6)	200 (9.4)	.269	12203 (18.6)	88 (10.1)	.244	12203 (18.6)	1275 (13.6)	.138	12203 (18.6)	78 (4.4)	.458
Anti-manic	71 (0.1)	18 (0.8)	.107	71 (0.1)	16 (1.8)	.177	71 (0.1)	51 (0.5)	.076	71 (0.1)	51 (2.9)	.229
Oral corticosteroid	7351 (11.2)	82 (3.8)	.282	7351 (11.2)	28 (3.2)	.313	7351 (11.2)	960 (10.2)	.032	7351 (11.2)	56 (3.1)	.317
NSAIDS	8394 (12.8)	272 (12.7)	.002	8394 (12.8)	146 (16.8)	.112	8394 (12.8)	1743 (18.6)	.158	8394 (12.8)	226 (12.7)	.004
PPI/H2 blocker	32161 (49.1)	519 (24.3)	.532	32161 (49.1)	222 (25.5)	.503	32161 (49.1)	3592 (38.2)	.220	32161 (49.1)	311 (17.5)	.713
Antibacterial	35171 (53.7)	471 (22.1)	.690	35171 (53.7)	169 (19.4)	.761	35171 (53.7)	3847 (41.0)	.257	35171 (53.7)	295 (16.6)	.844
Antifungal	667 (1.0)	7 (0.3)	.085	667 (1.0)	2 (0.2)	.100	667 (1.0)	148 (1.6)	.049	667 (1.0)	5 (0.3)	.092
Antiviral Drugs	2198 (3.4)	30 (1.4)	.128	2198 (3.4)	15 (1.7)	.104	2198 (3.4)	278 (3.0)	.023	2198 (3.4)	20 (1.1)	.151

SD, standardised difference; NSAIDS, non-steroid anti-inflammation drugs; PPI, proton pump inhibitor; H2 blocker, histamine-2 receptor blocker.

eTable 4. Baseline Characteristics of Included Patients before Propensity Score Matching (Amisulpride, Aripiprazole, Chlorpromazine and Olanzapine)

Version Date: 20191113

No. (%)	Amisulpride-haloperidol cohort			Aripiprazole-haloperidol cohort			Chlorpromazine-haloperidol cohort			Olanzapine-haloperidol cohort		
	Haloperidol	Amisulpride	SD	Haloperidol	Aripiprazole	SD	Haloperidol	Chlorpromazine	SD	Haloperidol	Olanzapine	SD
Comorbidities												
Schizophrenia	1141 (1.7)	226 (10.6)	.374	1141 (1.7)	50 (5.7)	.212	1141 (1.7)	353 (3.8)	.124	1141 (1.7)	195 (10.9)	.385
Bipolar disorder	338 (0.5)	37 (1.7)	.116	338 (0.5)	29 (3.3)	.206	338 (0.5)	144 (1.5)	.101	338 (0.5)	160 (9.0)	.406
Other psychoses	3606 (5.5)	123 (5.8)	.011	3606 (5.5)	45 (5.2)	.015	3606 (5.5)	416 (4.4)	.050	3606 (5.5)	182 (10.2)	.176
Major depressive disorder	2472 (3.8)	260 (12.2)	.314	2472 (3.8)	251 (28.9)	.722	2472 (3.8)	879 (9.4)	.227	2472 (3.8)	281 (15.8)	.413
Dementia	5154 (7.9)	156 (7.3)	.021	5154 (7.9)	11 (1.3)	.320	5154 (7.9)	92 (1.0)	.340	5154 (7.9)	11 (0.6)	.366
Anxiety disorder	2165 (3.3)	179 (8.4)	.218	2165 (3.3)	156 (17.9)	.489	2165 (3.3)	606 (6.5)	.146	2165 (3.3)	191 (10.7)	.294
Delusional disorder	542 (0.8)	47 (2.2)	.113	542 (0.8)	13 (1.5)	.062	542 (0.8)	66 (0.7)	.014	542 (0.8)	31 (1.7)	.081
Personality disorder	356 (0.5)	23 (1.1)	.060	356 (0.5)	23 (2.6)	.168	356 (0.5)	203 (2.2)	.140	356 (0.5)	39 (2.2)	.142
Post-traumatic stress disorder	40 (0.1)	4 (0.2)	.036	40 (0.1)	8 (0.9)	.123	40 (0.1)	39 (0.4)	.073	40 (0.1)	11 (0.6)	.096
Sleep disorder	180 (0.3)	11 (0.5)	.038	180 (0.3)	5 (0.6)	.046	180 (0.3)	36 (0.4)	.019	180 (0.3)	6 (0.3)	.011
Behavioural problem	79 (0.1)	9 (0.4)	.058	79 (0.1)	3 (0.3)	.047	79 (0.1)	32 (0.3)	.046	79 (0.1)	2 (0.1)	.002
Myocardial infarction	3394 (5.2)	38 (1.8)	.186	3394 (5.2)	10 (1.1)	.232	3394 (5.2)	258 (2.7)	.125	3394 (5.2)	7 (0.4)	.294
Arrhythmia	8780 (13.4)	115 (5.4)	.277	8780 (13.4)	37 (4.3)	.327	8780 (13.4)	452 (4.8)	.302	8780 (13.4)	26 (1.5)	.468
Other ischemic heart disease	9085 (13.9)	130 (6.1)	.262	9085 (13.9)	35 (4.0)	.350	9085 (13.9)	671 (7.1)	.221	9085 (13.9)	28 (1.6)	.473
Congestive heart disease	9218 (14.1)	92 (4.3)	.343	9218 (14.1)	26 (3.0)	.405	9218 (14.1)	381 (4.1)	.354	9218 (14.1)	18 (1.0)	.510
Hypertension	25484 (38.9)	349 (16.3)	.521	25484 (38.9)	98 (11.3)	.673	25484 (38.9)	1706 (18.2)	.472	25484 (38.9)	96 (5.4)	.882
Cerebrovascular	16235 (24.8)	236 (11.1)	.364	16235 (24.8)	35 (4.0)	.619	16235 (24.8)	1222 (13.0)	.304	16235 (24.8)	55 (3.1)	.660
Diabetes	13957 (21.3)	187 (8.8)	.357	13957 (21.3)	52 (6.0)	.458	13957 (21.3)	1129 (12.0)	.251	13957 (21.3)	46 (2.6)	.603
Chronic kidney disease	5674 (8.7)	20 (0.9)	.367	5674 (8.7)	7 (0.8)	.376	5674 (8.7)	581 (6.2)	.095	5674 (8.7)	8 (0.4)	.402
Hypothyroidism	1029 (1.6)	19 (0.9)	.062	1029 (1.6)	6 (0.7)	.083	1029 (1.6)	44 (0.5)	.110	1029 (1.6)	12 (0.7)	.085
Parkinson's disease	1205 (1.8)	50 (2.3)	.035	1205 (1.8)	8 (0.9)	.079	1205 (1.8)	46 (0.5)	.126	1205 (1.8)	24 (1.3)	.039
Hepatic disease	2681 (4.1)	48 (2.2)	.105	2681 (4.1)	17 (2.0)	.125	2681 (4.1)	336 (3.6)	.027	2681 (4.1)	23 (1.3)	.174
COPD	6378 (9.7)	59 (2.8)	.291	6378 (9.7)	15 (1.7)	.350	6378 (9.7)	333 (3.5)	.251	6378 (9.7)	23 (1.3)	.376
Suicidal attempt	1245 (1.9)	71 (3.3)	.089	1245 (1.9)	71 (8.2)	.289	1245 (1.9)	705 (7.5)	.267	1245 (1.9)	97 (5.4)	.189
Healthcare service use												
Inpatient admission, mean (SD)	2.43 (5.07)	0.82 (2.13)	.414	2.43 (5.07)	0.65 (1.52)	.476	2.43 (5.07)	1.96 (6.49)	.081	2.43 (5.07)	0.77 (2.11)	.426
Outpatient clinic appointment, mean (SD)	9.32 (12.54)	8.79 (16.19)	.036	9.32 (12.54)	9.44 (13.45)	.010	9.32 (12.54)	9.17 (15.41)	.011	9.32 (12.54)	6.44 (11.28)	.241
Emergency attendance, mean (SD)	2.38 (3.20)	1.26 (2.18)	.412	2.38 (3.20)	1.25 (2.59)	.390	2.38 (3.20)	2.01 (3.71)	.109	2.38 (3.20)	1.16 (2.19)	.445

SD, standardised difference; COPD, chronic obstructive pulmonary disease.

eTable 4. Baseline Characteristics of Included Patients before Propensity Score Matching (Amisulpride, Aripiprazole, Chlorpromazine and Olanzapine) (continued)

12

No. (%)	Quetiapine-haloperidol cohort			Risperidone-haloperidol cohort			Sulpiride-haloperidol cohort			Trifluoperazine-haloperidol cohort		
	Haloperidol	Quetiapine	SD	Haloperidol	Risperidone	SD	Haloperidol	Sulpiride	SD	Haloperidol	Trifluoperazir	SD
Demographic												
Male	29389 (44.9)	5935 (35.1)	.199	29389 (44.9)	7037 (41.8)	.062	29389 (44.9)	3944 (38.0)	.140	29389 (44.9)	2804 (43.3)	.032
Age, mean (SD)	73.77 (18.26)	59.95 (20.81)	.706	73.77 (18.26)	50.48 (22.13)	1.148	73.77 (18.26)	54.08 (20.19)	1.023	73.77 (18.26)	41.57 (14.52)	1.952
Medication use												
No. of recent prescriptions, mean (SD)	82.13 (122.72)	52.23 (92.65)	.275	82.13 (122.72)	29.78 (67.35)	.529	82.13 (122.72)	36.80 (65.48)	.461	82.13 (122.72)	14.86 (34.25)	.747
Antidepressant	8850 (13.5)	8899 (52.7)	.916	8850 (13.5)	4948 (29.4)	.394	8850 (13.5)	4644 (44.7)	.732	8850 (13.5)	1331 (20.5)	.188
Hypnotic/anxiolytic	12397 (18.9)	8642 (51.2)	.718	12397 (18.9)	5089 (30.2)	.264	12397 (18.9)	4291 (41.3)	.503	12397 (18.9)	1615 (24.9)	.145
Antiepileptic	4549 (6.9)	2937 (17.4)	.324	4549 (6.9)	1361 (8.1)	.043	4549 (6.9)	920 (8.9)	.071	4549 (6.9)	293 (4.5)	.104
Antidiabetic	14322 (21.9)	2156 (12.8)	.242	14322 (21.9)	1431 (8.5)	.379	14322 (21.9)	1000 (9.6)	.341	14322 (21.9)	269 (4.2)	.546
Drugs used in hypertension and heart failure	24877 (38.0)	3262 (19.3)	.422	24877 (38.0)	2107 (12.5)	.613	24877 (38.0)	1512 (14.6)	.552	24877 (38.0)	287 (4.4)	.900
Antiplatelet	25168 (38.4)	3343 (19.8)	.419	25168 (38.4)	1938 (11.5)	.654	25168 (38.4)	1363 (13.1)	.604	25168 (38.4)	178 (2.7)	.983
Calcium channel blockers	26879 (41.0)	4275 (25.3)	.338	26879 (41.0)	2599 (15.4)	.593	26879 (41.0)	1725 (16.6)	.560	26879 (41.0)	343 (5.3)	.935
Loop diuretics	15026 (22.9)	1207 (7.1)	.453	15026 (22.9)	781 (4.6)	.551	15026 (22.9)	517 (5.0)	.537	15026 (22.9)	65 (1.0)	.718
Other diuretics	7232 (11.0)	858 (5.1)	.220	7232 (11.0)	599 (3.6)	.291	7232 (11.0)	468 (4.5)	.246	7232 (11.0)	133 (2.1)	.369
Beta blockers	19003 (29.0)	3671 (21.7)	.168	19003 (29.0)	2168 (12.9)	.405	19003 (29.0)	1817 (17.5)	.275	19003 (29.0)	509 (7.9)	.567
Antiarrhythmic	1759 (2.7)	133 (0.8)	.146	1759 (2.7)	85 (0.5)	.175	1759 (2.7)	57 (0.5)	.170	1759 (2.7)	16 (0.2)	.204
Digoxin	3804 (5.8)	278 (1.6)	.221	3804 (5.8)	216 (1.3)	.247	3804 (5.8)	171 (1.6)	.221	3804 (5.8)	15 (0.2)	.330
Nitrate	11261 (17.2)	1150 (6.8)	.324	11261 (17.2)	737 (4.4)	.422	11261 (17.2)	573 (5.5)	.374	11261 (17.2)	91 (1.4)	.565
Anticoagulant	5751 (8.8)	456 (2.7)	.264	5751 (8.8)	295 (1.8)	.319	5751 (8.8)	217 (2.1)	.298	5751 (8.8)	41 (0.6)	.392
Peripheral vasodilator	1661 (2.5)	337 (2.0)	.036	1661 (2.5)	344 (2.0)	.033	1661 (2.5)	180 (1.7)	.056	1661 (2.5)	34 (0.5)	.164
Lipid lowering drugs	12203 (18.6)	2473 (14.6)	.107	12203 (18.6)	1352 (8.0)	.316	12203 (18.6)	918 (8.8)	.287	12203 (18.6)	150 (2.3)	.553
Anti-manic	71 (0.1)	214 (1.3)	.141	71 (0.1)	95 (0.6)	.079	71 (0.1)	48 (0.5)	.066	71 (0.1)	40 (0.6)	.085
Oral corticosteroid	7351 (11.2)	974 (5.8)	.197	7351 (11.2)	561 (3.3)	.307	7351 (11.2)	437 (4.2)	.265	7351 (11.2)	136 (2.1)	.372
NSAIDS	8394 (12.8)	3244 (19.2)	.175	8394 (12.8)	2443 (14.5)	.049	8394 (12.8)	1954 (18.8)	.165	8394 (12.8)	877 (13.5)	.021
PPI/H2 blocker	32161 (49.1)	6612 (39.2)	.201	32161 (49.1)	4117 (24.4)	.529	32161 (49.1)	2959 (28.5)	.432	32161 (49.1)	805 (12.4)	.866
Antibacterial	35171 (53.7)	5133 (30.4)	.485	35171 (53.7)	3685 (21.9)	.695	35171 (53.7)	2642 (25.4)	.603	35171 (53.7)	1044 (16.1)	.858
Antifungal	667 (1.0)	72 (0.4)	.070	667 (1.0)	34 (0.2)	.105	667 (1.0)	29 (0.3)	.092	667 (1.0)	9 (0.1)	.116
Antiviral Drugs	2198 (3.4)	362 (2.1)	.074	2198 (3.4)	242 (1.4)	.126	2198 (3.4)	155 (1.5)	.121	2198 (3.4)	44 (0.7)	.191

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96 SD, standardised difference; NSAIDS, non-steroid anti-inflammation drugs; PPI, proton pump inhibitor; H2 blocker, histamine-2 receptor blocker.
97 **eTable 5. Baseline Characteristics of Included Patients before Propensity Score Matching (Quetiapine, Risperidone, Sulpiride, and Trifluoperazine)**

No. (%)	Quetiapine-haloperidol cohort			Risperidone-haloperidol cohort			Sulpiride-haloperidol cohort			Trifluoperazine-haloperidol cohort		
	Haloperidol	Quetiapine	SD	Haloperidol	Risperidone	SD	Haloperidol	Sulpiride	SD	Haloperidol	Trifluoperazir	SD
Comorbidities												
Schizophrenia	1141 (1.7)	341 (2.0)	.020	1141 (1.7)	891 (5.3)	.194	1141 (1.7)	532 (5.1)	.187	1141 (1.7)	872 (13.5)	.453
Bipolar disorder	338 (0.5)	544 (3.2)	.201	338 (0.5)	330 (2.0)	.131	338 (0.5)	146 (1.4)	.091	338 (0.5)	156 (2.4)	.158
Other psychoses	3606 (5.5)	741 (4.4)	.051	3606 (5.5)	1667 (9.9)	.165	3606 (5.5)	653 (6.3)	.033	3606 (5.5)	946 (14.6)	.306
Major depressive disorder	2472 (3.8)	3765 (22.3)	.572	2472 (3.8)	1950 (11.6)	.296	2472 (3.8)	1938 (18.7)	.486	2472 (3.8)	612 (9.4)	.230
Dementia	5154 (7.9)	1306 (7.7)	.005	5154 (7.9)	852 (5.1)	.114	5154 (7.9)	501 (4.8)	.125	5154 (7.9)	28 (0.4)	.379
Anxiety disorder	2165 (3.3)	2644 (15.7)	.431	2165 (3.3)	1709 (10.1)	.276	2165 (3.3)	1565 (15.1)	.416	2165 (3.3)	529 (8.2)	.210
Delusional disorder	542 (0.8)	129 (0.8)	.007	542 (0.8)	391 (2.3)	.120	542 (0.8)	200 (1.9)	.094	542 (0.8)	205 (3.2)	.168
Personality disorder	356 (0.5)	327 (1.9)	.126	356 (0.5)	296 (1.8)	.114	356 (0.5)	178 (1.7)	.111	356 (0.5)	147 (2.3)	.147
Post-traumatic stress disorder	40 (0.1)	121 (0.7)	.105	40 (0.1)	53 (0.3)	.059	40 (0.1)	58 (0.6)	.090	40 (0.1)	17 (0.3)	.050
Sleep disorder	180 (0.3)	93 (0.6)	.043	180 (0.3)	58 (0.3)	.013	180 (0.3)	72 (0.7)	.060	180 (0.3)	12 (0.2)	.019
Behavioural problem	79 (0.1)	58 (0.3)	.046	79 (0.1)	75 (0.4)	.061	79 (0.1)	44 (0.4)	.058	79 (0.1)	24 (0.4)	.051
Myocardial infarction	3394 (5.2)	316 (1.9)	.180	3394 (5.2)	195 (1.2)	.231	3394 (5.2)	118 (1.1)	.233	3394 (5.2)	16 (0.2)	.307
Arrhythmia	8780 (13.4)	1106 (6.6)	.230	8780 (13.4)	678 (4.0)	.337	8780 (13.4)	480 (4.6)	.310	8780 (13.4)	62 (1.0)	.497
Other ischemic heart disease	9085 (13.9)	1151 (6.8)	.233	9085 (13.9)	710 (4.2)	.342	9085 (13.9)	534 (5.1)	.301	9085 (13.9)	70 (1.1)	.501
Congestive heart disease	9218 (14.1)	836 (5.0)	.315	9218 (14.1)	561 (3.3)	.388	9218 (14.1)	352 (3.4)	.385	9218 (14.1)	38 (0.6)	.536
Hypertension	25484 (38.9)	3679 (21.8)	.379	25484 (38.9)	2267 (13.5)	.605	25484 (38.9)	1558 (15.0)	.559	25484 (38.9)	225 (3.5)	.962
Cerebrovascular	16235 (24.8)	2108 (12.5)	.320	16235 (24.8)	1223 (7.3)	.492	16235 (24.8)	958 (9.2)	.423	16235 (24.8)	104 (1.6)	.729
Diabetes	13957 (21.3)	1895 (11.2)	.276	13957 (21.3)	1233 (7.3)	.408	13957 (21.3)	846 (8.1)	.378	13957 (21.3)	187 (2.9)	.589
Chronic kidney disease	5674 (8.7)	328 (1.9)	.303	5674 (8.7)	193 (1.1)	.353	5674 (8.7)	98 (0.9)	.367	5674 (8.7)	19 (0.3)	.413
Hypothyroidism	1029 (1.6)	181 (1.1)	.044	1029 (1.6)	126 (0.7)	.077	1029 (1.6)	85 (0.8)	.069	1029 (1.6)	26 (0.4)	.119
Parkinson's disease	1205 (1.8)	1101 (6.5)	.236	1205 (1.8)	179 (1.1)	.065	1205 (1.8)	204 (2.0)	.009	1205 (1.8)	20 (0.3)	.149
Hepatic disease	2681 (4.1)	557 (3.3)	.042	2681 (4.1)	349 (2.1)	.117	2681 (4.1)	255 (2.5)	.092	2681 (4.1)	60 (0.9)	.203
COPD	6378 (9.7)	751 (4.4)	.207	6378 (9.7)	482 (2.9)	.286	6378 (9.7)	320 (3.1)	.274	6378 (9.7)	56 (0.9)	.404
Suicidal attempt	1245 (1.9)	1180 (7.0)	.249	1245 (1.9)	808 (4.8)	.161	1245 (1.9)	526 (5.1)	.173	1245 (1.9)	355 (5.5)	.191
Healthcare service use												
Inpatient admission, mean (SD)	2.43 (5.07)	1.16 (2.79)	.310	2.43 (5.07)	0.89 (2.00)	.399	2.43 (5.07)	0.92 (2.01)	.392	2.43 (5.07)	0.82 (1.93)	.419
Outpatient clinic appointment, mean (SD)	9.32 (12.54)	11.63 (14.84)	.168	9.32 (12.54)	7.58 (13.87)	.131	9.32 (12.54)	10.07 (14.42)	.056	9.32 (12.54)	5.53 (13.15)	.294
Emergency attendance, mean (SD)	2.38 (3.20)	1.60 (2.86)	.260	2.38 (3.20)	1.41 (2.50)	.340	2.38 (3.20)	1.73 (3.39)	.199	2.38 (3.20)	1.57 (2.89)	.269

SD, standardised difference; COPD, chronic obstructive pulmonary disease.

eTable 5. Baseline Characteristics of Included Patients before Propensity Score Matching (Quetiapine, Risperidone, Sulpiride, and Trifluoperazine) (continued)

Version Date: 20191113

No. (%)	Amisulpride-haloperidol cohort			Aripiprazole-haloperidol cohort			Chlorpromazine-haloperidol cohort			Olanzapine-haloperidol cohort		
	Haloperidol	Amisulpride	SD	Haloperidol	Aripiprazole	SD	Haloperidol	Chlorpromazine	SD	Haloperidol	Olanzapine	SD
Demographic												
Male	809.0 (40.2)	809.0 (40.2)	<.001	225.0 (34.7)	225.0 (34.7)	<.001	6588.0 (75.4)	6588.0 (75.4)	<.001	647.0 (42.3)	647.0 (42.3)	.001
Age, mean (SD)	55.82 (23.16)	55.75 (23.16)	.003	46.67 (19.94)	46.66 (19.81)	<.001	54.54 (17.96)	54.54 (17.89)	<.001	43.50 (17.15)	43.52 (17.23)	.001
Medication use												
No. of recent prescriptions, mean (SD)	31.11 (75.76)	34.62 (67.08)	.049	28.90 (81.91)	35.27 (73.93)	.082	61.45 (116.15)	56.27 (113.01)	.045	21.49 (58.16)	23.35 (58.27)	.032
Antidepressant	492.0 (24.5)	529.0 (26.3)	.042	258.0 (39.8)	275.0 (42.4)	.053	1599.0 (18.3)	1507.0 (17.3)	.028	361.5 (23.6)	400.0 (26.1)	.058
Hypnotic/anxiolytic	506.5 (25.2)	544.0 (27.1)	.042	217.0 (33.4)	239.0 (36.8)	.071	1984.5 (22.7)	1867.0 (21.4)	.033	391.5 (25.6)	445.0 (29.1)	.078
Antiepileptic	136.5 (6.8)	150.0 (7.5)	.026	70.0 (10.8)	86.0 (13.3)	.076	974.0 (11.2)	898.0 (10.3)	.028	160.5 (10.5)	164.0 (10.7)	.007
Antidiabetic	230.5 (11.5)	231.0 (11.5)	.001	43.5 (6.7)	53.0 (8.2)	.056	1426.2 (16.3)	1342.0 (15.4)	.026	58.0 (3.8)	58.0 (3.8)	<.001
Drugs used in hypertension and heart failure	282.5 (14.1)	328.0 (16.3)	.063	56.5 (8.7)	86.0 (13.3)	.146	2159.4 (24.7)	2118.0 (24.2)	.011	74.2 (4.9)	84.0 (5.5)	.029
Antiplatelet	299.5 (14.9)	332.0 (16.5)	.044	45.0 (6.9)	77.0 (11.9)	.170	1790.5 (20.5)	1726.0 (19.8)	.018	59.7 (3.9)	79.0 (5.2)	.060
Calcium channel blockers	337.0 (16.8)	395.0 (19.7)	.075	66.5 (10.2)	97.0 (14.9)	.142	2098.7 (24.0)	2090.0 (23.9)	.002	102.9 (6.7)	130.0 (8.5)	.067
Loop diuretics	121.0 (6.0)	131.0 (6.5)	.021	21.0 (3.2)	27.0 (4.2)	.049	929.7 (10.6)	860.0 (9.8)	.026	30.5 (2.0)	26.0 (1.7)	.022
Other diuretics	96.0 (4.8)	110.0 (5.5)	.032	17.0 (2.6)	19.0 (2.9)	.019	669.0 (7.7)	687.0 (7.9)	.008	27.5 (1.8)	35.0 (2.3)	.035
Beta blockers	310.0 (15.4)	343.0 (17.1)	.045	73.5 (11.3)	107.0 (16.5)	.150	2040.7 (23.4)	1941.0 (22.2)	.027	123.2 (8.1)	144.0 (9.4)	.048
Antiarrhythmic	13.5 (0.7)	19.0 (0.9)	.031	6.0 (0.9)	8.0 (1.2)	.030	152.0 (1.7)	129.0 (1.5)	.021	2.5 (0.2)	4.0 (0.3)	.021
Digoxin	43.5 (2.2)	39.0 (1.9)	.016	6.0 (0.9)	8.0 (1.2)	.030	172.0 (2.0)	173.0 (2.0)	.001	10.0 (0.7)	12.0 (0.8)	.015
Nitrate	132.5 (6.6)	149.0 (7.4)	.032	15.0 (2.3)	27.0 (4.2)	.105	780.5 (8.9)	779.0 (8.9)	.001	28.0 (1.8)	36.0 (2.4)	.036
Anticoagulant	53.0 (2.6)	51.0 (2.5)	.006	11.0 (1.7)	17.0 (2.6)	.064	644.5 (7.4)	600.0 (6.9)	.020	17.5 (1.1)	14.0 (0.9)	.023
Peripheral vasodilator	57.0 (2.8)	65.0 (3.2)	.023	4.5 (0.7)	6.0 (0.9)	.026	94.5 (1.1)	92.0 (1.1)	.003	5.0 (0.3)	9.0 (0.6)	.039
Lipid lowering drugs	193.0 (9.6)	195.0 (9.7)	.003	46.0 (7.1)	66.0 (10.2)	.110	1280.0 (14.7)	1228.0 (14.1)	.017	58.5 (3.8)	71.0 (4.6)	.040
Anti-manic	10.0 (0.5)	8.0 (0.4)	.015	7.0 (1.1)	6.0 (0.9)	.015	31.0 (0.4)	29.0 (0.3)	.004	20.5 (1.3)	18.0 (1.2)	.015
Oral corticosteroid	68.5 (3.4)	81.0 (4.0)	.033	15.5 (2.4)	23.0 (3.5)	.068	898.7 (10.3)	908.0 (10.4)	.003	56.5 (3.7)	53.0 (3.5)	.012
NSAIDS	237.0 (11.8)	251.0 (12.5)	.021	85.0 (13.1)	111.0 (17.1)	.112	1460.7 (16.7)	1452.0 (16.6)	.003	161.2 (10.5)	190.0 (12.4)	.059
PPI/H2 blocker	458.5 (22.8)	509.0 (25.3)	.059	122.0 (18.8)	175.0 (27.0)	.195	3317.5 (38.0)	3345.0 (38.3)	.006	215.7 (14.1)	276.0 (18.0)	.107
Antibacterial	403.5 (20.1)	465.0 (23.1)	.074	114.5 (17.6)	151.0 (23.3)	.140	3709.7 (42.5)	3653.0 (41.8)	.013	231.4 (15.1)	267.0 (17.4)	.063
Antifungal	5.5 (0.3)	7.0 (0.3)	.013	1.5 (0.2)	2.0 (0.3)	.015	143.0 (1.6)	147.0 (1.7)	.004	4.0 (0.3)	5.0 (0.3)	.012
Antiviral Drugs	23.0 (1.1)	29.0 (1.4)	.026	12.5 (1.9)	15.0 (2.3)	.027	297.7 (3.4)	270.0 (3.1)	.018	17.5 (1.1)	19.0 (1.2)	.009

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103 SD, standardised difference; NSAIDS, non-steroid anti-inflammation drugs; PPI, proton pump inhibitor; H2 blocker, histamine-2 receptor blocker.

104 **eTable 6. Baseline Characteristics of Included Patients after Propensity Score Matching (Amisulpride, Aripiprazole, Chlorpromazine and Olanzapine)**

Version Date: 20191113

No. (%)	Amisulpride-haloperidol cohort			Aripiprazole-haloperidol cohort			Chlorpromazine-haloperidol cohort			Olanzapine-haloperidol cohort		
	Haloperidol	Amisulpride	SMD	Haloperidol	Aripiprazole	SMD	Haloperidol	Chlorpromazine	SMD	Haloperidol	Olanzapine	SMD
Comorbidities												
Schizophrenia	172.5 (8.6)	167.0 (8.3)	.010	36.0 (5.5)	41.0 (6.3)	.033	365.5 (4.2)	335.0 (3.8)	.018	147.0 (9.6)	163.0 (10.6)	.034
Bipolar disorder	35.5 (1.8)	35.0 (1.7)	.002	14.0 (2.2)	12.0 (1.8)	.022	127.5 (1.5)	114.0 (1.3)	.013	88.5 (5.8)	82.0 (5.4)	.019
Other psychoses	121.0 (6.0)	118.0 (5.9)	.006	42.5 (6.5)	43.0 (6.6)	.003	442.0 (5.1)	411.0 (4.7)	.016	164.5 (10.8)	160.0 (10.5)	.010
Major depressive disorder	184.5 (9.2)	206.0 (10.2)	.036	127.0 (19.6)	126.0 (19.4)	.004	610.5 (7.0)	547.0 (6.3)	.029	186.0 (12.2)	205.0 (13.4)	.037
Dementia	132.0 (6.6)	153.0 (7.6)	.041	11.5 (1.8)	11.0 (1.7)	.006	127.5 (1.5)	92.0 (1.1)	.037	9.2 (0.6)	11.0 (0.7)	.014
Anxiety disorder	132.0 (6.6)	155.0 (7.7)	.044	78.5 (12.1)	89.0 (13.7)	.048	487.0 (5.6)	443.0 (5.1)	.022	136.5 (8.9)	142.0 (9.3)	.012
Delusional disorder	39.0 (1.9)	36.0 (1.8)	.011	6.0 (0.9)	12.0 (1.8)	.079	75.5 (0.9)	65.0 (0.7)	.013	20.0 (1.3)	29.0 (1.9)	.047
Personality disorder	19.5 (1.0)	21.0 (1.0)	.007	8.5 (1.3)	13.0 (2.0)	.054	149.5 (1.7)	138.0 (1.6)	.010	30.5 (2.0)	34.0 (2.2)	.016
Post-traumatic stress disorder	1.0 (0.0)	4.0 (0.2)	.042	1.0 (0.2)	2.0 (0.3)	.032	17.0 (0.2)	16.0 (0.2)	.003	3.0 (0.2)	4.0 (0.3)	.014
Sleep disorder	7.5 (0.4)	9.0 (0.4)	.012	1.5 (0.2)	3.0 (0.5)	.039	29.5 (0.3)	32.0 (0.4)	.005	5.5 (0.4)	6.0 (0.4)	.005
Behavioural problem	9.0 (0.4)	7.0 (0.3)	.016	1.5 (0.2)	2.0 (0.3)	.015	27.5 (0.3)	27.0 (0.3)	.001	3.5 (0.2)	1.0 (0.1)	.043
Myocardial infarction	30.5 (1.5)	37.0 (1.8)	.025	5.0 (0.8)	9.0 (1.4)	.060	273.5 (3.1)	254.0 (2.9)	.013	4.0 (0.3)	7.0 (0.5)	.033
Arrhythmia	104.0 (5.2)	115.0 (5.7)	.024	22.5 (3.5)	32.0 (4.9)	.073	419.5 (4.8)	447.0 (5.1)	.014	24.4 (1.6)	25.0 (1.6)	.003
Other ischemic heart disease	108.5 (5.4)	130.0 (6.5)	.045	15.5 (2.4)	31.0 (4.8)	.129	638.0 (7.3)	652.0 (7.5)	.006	14.0 (0.9)	26.0 (1.7)	.069
Congestive heart disease	77.5 (3.9)	91.0 (4.5)	.034	12.5 (1.9)	23.0 (3.5)	.099	375.7 (4.3)	380.0 (4.3)	.002	11.5 (0.8)	18.0 (1.2)	.043
Hypertension	301.5 (15.0)	348.0 (17.3)	.063	58.5 (9.0)	90.0 (13.9)	.153	1688.2 (19.3)	1681.0 (19.2)	.002	62.9 (4.1)	88.0 (5.7)	.076
Cerebrovascular	203.5 (10.1)	236.0 (11.7)	.052	19.0 (2.9)	35.0 (5.4)	.124	1319.0 (15.1)	1211.0 (13.9)	.035	39.2 (2.6)	51.0 (3.3)	.045
Diabetes	172.0 (8.6)	185.0 (9.2)	.023	34.5 (5.3)	46.0 (7.1)	.074	1188.5 (13.6)	1100.0 (12.6)	.030	44.2 (2.9)	46.0 (3.0)	.007
Chronic kidney disease	25.0 (1.2)	20.0 (1.0)	.024	4.0 (0.6)	7.0 (1.1)	.050	630.5 (7.2)	574.0 (6.6)	.026	15.0 (1.0)	8.0 (0.5)	.053
Hypothyroidism	14.5 (0.7)	17.0 (0.8)	.014	2.0 (0.3)	6.0 (0.9)	.079	45.0 (0.5)	44.0 (0.5)	.002	8.5 (0.6)	10.0 (0.7)	.013
Parkinson's disease	43.5 (2.2)	46.0 (2.3)	.008	8.5 (1.3)	8.0 (1.2)	.007	63.0 (0.7)	46.0 (0.5)	.025	20.5 (1.3)	21.0 (1.4)	.003
Hepatic disease	36.0 (1.8)	47.0 (2.3)	.038	12.5 (1.9)	17.0 (2.6)	.047	336.0 (3.8)	321.0 (3.7)	.009	10.5 (0.7)	18.0 (1.2)	.051
COPD	45.5 (2.3)	59.0 (2.9)	.042	14.0 (2.2)	13.0 (2.0)	.011	351.7 (4.0)	330.0 (3.8)	.013	19.0 (1.2)	20.0 (1.3)	.006
Suicidal attempt	71.0 (3.5)	66.0 (3.3)	.014	45.0 (6.9)	44.0 (6.8)	.006	507.5 (5.8)	468.0 (5.4)	.020	71.5 (4.7)	78.0 (5.1)	.020
Healthcare service use												
Inpatient admission, mean (SD)	0.83 (1.21)	0.86 (2.19)	.016	0.64 (1.04)	0.76 (1.70)	.083	2.13 (6.41)	2.00 (6.67)	.020	0.78 (1.32)	0.81 (2.24)	.020
Outpatient clinic appointment, mean (SD)	6.84 (12.51)	7.85 (11.32)	.085	6.95 (12.78)	8.67 (13.53)	.130	8.64 (15.05)	8.44 (12.87)	.014	5.89 (12.21)	6.27 (11.56)	.032
Emergency attendance, mean (SD)	1.32 (1.92)	1.31 (2.22)	.005	1.18 (1.74)	1.32 (2.68)	.061	2.08 (3.07)	1.98 (3.63)	.031	1.14 (1.60)	1.22 (2.29)	.039

SD, standardised difference; COPD, chronic obstructive pulmonary disease.

eTable 6. Baseline Characteristics of Included Patients after Propensity Score Matching (Amisulpride, Aripiprazole, Chlorpromazine and Olanzapine) (continued)

Version Date: 20191113

No. (%)	Quetiapine-haloperidol cohort			Risperidone-haloperidol cohort			Sulpiride-haloperidol cohort			Trifluoperazine-haloperidol cohort		
	Haloperidol	Quetiapine	SD	Haloperidol	Risperidone	SD	Haloperidol	Sulpiride	SD	Haloperidol	Trifluoperazir	SD
Demographic												
Male	4163.0 (39.2)	4163.0 (39.2)	<.001	4402.0 (40.6)	4402.0 (40.6)	<.001	3429.0 (40.5)	3429.0 (40.5)	<.001	2703.0 (44.2)	2703.0 (44.2)	<.001
Age, mean (SD)	66.86 (20.88)	66.85 (20.85)	<.001	57.96 (22.71)	57.91 (22.71)	.003	56.18 (21.16)	56.17 (21.15)	.001	41.69 (14.82)	41.67 (14.73)	.001
Medication use												
No. of recent prescriptions, mean (SD)	59.64 (99.45)	58.21 (107.50)	.014	36.86 (71.06)	38.06 (73.62)	.017	37.42 (69.82)	37.06 (69.97)	.005	14.07 (32.96)	14.99 (34.98)	.027
Antidepressant	3673.0 (34.6)	3525.0 (33.2)	.029	2485.0 (22.9)	2577.0 (23.8)	.020	2707.5 (32.0)	2760.0 (32.6)	.013	1098.0 (17.9)	1159.0 (18.9)	.026
Hypnotic/anxiolytic	4058.5 (38.2)	3960.0 (37.3)	.019	2870.0 (26.5)	3001.0 (27.7)	.027	2755.2 (32.6)	2772.0 (32.8)	.004	1388.0 (22.7)	1434.0 (23.4)	.018
Antiepileptic	1249.5 (11.8)	1166.0 (11.0)	.025	785.0 (7.2)	832.0 (7.7)	.017	697.5 (8.2)	672.0 (7.9)	.011	290.5 (4.7)	289.0 (4.7)	.001
Antidiabetic	1714.5 (16.1)	1722.0 (16.2)	.002	1271.5 (11.7)	1304.0 (12.0)	.009	941.0 (11.1)	900.0 (10.6)	.016	242.5 (4.0)	268.0 (4.4)	.021
Drugs used in hypertension and heart failure	2716.0 (25.6)	2747.0 (25.8)	.007	1856.0 (17.1)	1989.0 (18.4)	.032	1374.2 (16.2)	1411.0 (16.7)	.012	246.5 (4.0)	286.0 (4.7)	.032
Antiplatelet	2865.5 (27.0)	2917.0 (27.4)	.011	1816.5 (16.8)	1894.0 (17.5)	.019	1282.4 (15.2)	1313.0 (15.5)	.010	146.5 (2.4)	178.0 (2.9)	.032
Calcium channel blockers	3388.5 (31.9)	3505.0 (33.0)	.023	2270.5 (21.0)	2441.0 (22.5)	.038	1565.5 (18.5)	1606.0 (19.0)	.012	300.0 (4.9)	341.0 (5.6)	.030
Loop diuretics	1140.0 (10.7)	1140.0 (10.7)	<.001	840.0 (7.8)	773.0 (7.1)	.024	523.2 (6.2)	504.0 (6.0)	.010	57.5 (0.9)	65.0 (1.1)	.012
Other diuretics	710.0 (6.7)	716.0 (6.7)	.002	556.0 (5.1)	567.0 (5.2)	.005	403.2 (4.8)	431.0 (5.1)	.015	109.0 (1.8)	128.0 (2.1)	.023
Beta blockers	2468.0 (23.2)	2375.0 (22.3)	.021	1710.0 (15.8)	1807.0 (16.7)	.024	1476.5 (17.5)	1436.0 (17.0)	.013	429.0 (7.0)	470.0 (7.7)	.026
Antiarrhythmic	126.5 (1.2)	120.0 (1.1)	.006	88.0 (0.8)	85.0 (0.8)	.003	57.5 (0.7)	56.0 (0.7)	.002	12.5 (0.2)	16.0 (0.3)	.012
Digoxin	255.5 (2.4)	264.0 (2.5)	.005	219.5 (2.0)	214.0 (2.0)	.004	162.0 (1.9)	169.0 (2.0)	.006	13.5 (0.2)	15.0 (0.2)	.005
Nitrate	1005.0 (9.5)	1009.0 (9.5)	.001	703.5 (6.5)	717.0 (6.6)	.005	517.2 (6.1)	543.0 (6.4)	.013	72.5 (1.2)	87.0 (1.4)	.021
Anticoagulant	416.5 (3.9)	415.0 (3.9)	.001	285.5 (2.6)	289.0 (2.7)	.002	205.0 (2.4)	214.0 (2.5)	.007	38.0 (0.6)	41.0 (0.7)	.006
Peripheral vasodilator	289.0 (2.7)	283.0 (2.7)	.003	303.0 (2.8)	322.0 (3.0)	.010	153.0 (1.8)	166.0 (2.0)	.011	31.0 (0.5)	32.0 (0.5)	.002
Lipid lowering drugs	1867.0 (17.6)	1902.0 (17.9)	.009	1156.5 (10.7)	1247.0 (11.5)	.027	846.0 (10.0)	824.0 (9.7)	.009	124.5 (2.0)	148.0 (2.4)	.026
Anti-manic	52.0 (0.5)	33.0 (0.3)	.028	43.5 (0.4)	42.0 (0.4)	.002	40.5 (0.5)	32.0 (0.4)	.015	31.5 (0.5)	32.0 (0.5)	.001
Oral corticosteroid	741.0 (7.0)	727.0 (6.8)	.005	483.0 (4.5)	498.0 (4.6)	.007	386.5 (4.6)	393.0 (4.6)	.004	122.5 (2.0)	135.0 (2.2)	.014
NSAIDS	1599.5 (15.0)	1503.0 (14.1)	.026	1404.5 (13.0)	1530.0 (14.1)	.034	1365.2 (16.1)	1349.0 (15.9)	.005	779.5 (12.7)	809.0 (13.2)	.014
PPI/H2 blocker	4346.5 (40.9)	4396.0 (41.4)	.009	2984.5 (27.5)	3274.0 (30.2)	.059	2266.9 (26.8)	2380.0 (28.1)	.030	713.5 (11.7)	791.0 (12.9)	.039
Antibacterial	3886.5 (36.6)	3927.0 (36.9)	.008	2936.5 (27.1)	3162.0 (29.2)	.046	2223.9 (26.3)	2356.0 (27.8)	.035	968.0 (15.8)	1031.0 (16.8)	.028
Antifungal	66.5 (0.6)	58.0 (0.5)	.010	28.0 (0.3)	34.0 (0.3)	.010	27.5 (0.3)	28.0 (0.3)	.001	5.5 (0.1)	9.0 (0.1)	.017
Antiviral Drugs	268.5 (2.5)	268.0 (2.5)	<.001	182.0 (1.7)	194.0 (1.8)	.008	132.7 (1.6)	140.0 (1.7)	.007	40.0 (0.7)	44.0 (0.7)	.008

SD, standardised difference; NSAIDS, non-steroid anti-inflammation drugs; PPI, proton pump inhibitor; H2 blocker, histamine-2 receptor blocker.

eTable 7. Baseline Characteristics of Included Patients after Propensity Score Matching (Quetiapine, Risperidone, Sulpiride, and Trifluoperazine)

Version Date: 20191113

No. (%)	Quetiapine-haloperidol cohort			Risperidone-haloperidol cohort			Sulpiride-haloperidol cohort			Trifluoperazine-haloperidol cohort		
	Haloperidol	Quetiapine	SD	Haloperidol	Risperidone	SD	Haloperidol	Sulpiride	SD	Haloperidol	Trifluoperazir	SD
Comorbidities												
Schizophrenia	235.0 (2.2)	246.0 (2.3)	.007	495.0 (4.6)	498.0 (4.6)	.001	515.5 (6.1)	467.0 (5.5)	.025	530.5 (8.7)	653.0 (10.7)	.068
Bipolar disorder	186.5 (1.8)	148.0 (1.4)	.029	162.0 (1.5)	148.0 (1.4)	.011	135.5 (1.6)	118.0 (1.4)	.017	147.5 (2.4)	137.0 (2.2)	.011
Other psychoses	549.0 (5.2)	554.0 (5.2)	.002	1038.5 (9.6)	964.0 (8.9)	.024	646.2 (7.6)	602.0 (7.1)	.020	880.5 (14.4)	863.0 (14.1)	.008
Major depressive disorder	1234.5 (11.6)	1138.0 (10.7)	.029	899.0 (8.3)	886.0 (8.2)	.004	989.5 (11.7)	1033.0 (12.2)	.016	480.5 (7.9)	523.0 (8.5)	.025
Dementia	1061.5 (10.0)	1160.0 (10.9)	.030	739.0 (6.8)	834.0 (7.7)	.034	446.0 (5.3)	497.0 (5.9)	.026	19.0 (0.3)	28.0 (0.5)	.024
Anxiety disorder	1002.5 (9.4)	918.0 (8.6)	.028	763.0 (7.0)	757.0 (7.0)	.002	800.5 (9.5)	813.0 (9.6)	.005	395.0 (6.5)	409.0 (6.7)	.009
Delusional disorder	96.0 (0.9)	99.0 (0.9)	.003	207.0 (1.9)	206.0 (1.9)	.001	187.5 (2.2)	169.0 (2.0)	.015	138.5 (2.3)	154.0 (2.5)	.017
Personality disorder	128.0 (1.2)	110.0 (1.0)	.016	145.5 (1.3)	151.0 (1.4)	.004	135.0 (1.6)	136.0 (1.6)	.001	137.5 (2.2)	134.0 (2.2)	.004
Post-traumatic stress disorder	24.0 (0.2)	12.0 (0.1)	.027	18.0 (0.2)	16.0 (0.1)	.005	21.5 (0.3)	16.0 (0.2)	.014	13.0 (0.2)	14.0 (0.2)	.003
Sleep disorder	45.0 (0.4)	49.0 (0.5)	.006	36.5 (0.3)	38.0 (0.4)	.002	46.5 (0.5)	39.0 (0.5)	.013	11.0 (0.2)	11.0 (0.2)	<.001
Behavioural problem	24.0 (0.2)	20.0 (0.2)	.008	37.0 (0.3)	30.0 (0.3)	.012	33.0 (0.4)	27.0 (0.3)	.012	26.0 (0.4)	23.0 (0.4)	.008
Myocardial infarction	286.5 (2.7)	285.0 (2.7)	.001	194.5 (1.8)	191.0 (1.8)	.002	119.5 (1.4)	116.0 (1.4)	.004	17.0 (0.3)	16.0 (0.3)	.003
Arrhythmia	915.0 (8.6)	972.0 (9.1)	.019	632.5 (5.8)	640.0 (5.9)	.003	430.0 (5.1)	459.0 (5.4)	.015	57.0 (0.9)	62.0 (1.0)	.008
Other ischemic heart disease	963.5 (9.1)	1000.0 (9.4)	.012	665.0 (6.1)	692.0 (6.4)	.010	486.5 (5.8)	507.0 (6.0)	.010	58.0 (0.9)	70.0 (1.1)	.019
Congestive heart disease	746.5 (7.0)	787.0 (7.4)	.015	577.5 (5.3)	551.0 (5.1)	.011	323.2 (3.8)	349.0 (4.1)	.016	32.0 (0.5)	38.0 (0.6)	.013
Hypertension	3002.5 (28.3)	3127.0 (29.4)	.026	2047.0 (18.9)	2172.0 (20.0)	.029	1404.9 (16.6)	1473.0 (17.4)	.021	194.0 (3.2)	222.0 (3.6)	.025
Cerebrovascular	1860.5 (17.5)	1852.0 (17.4)	.002	1181.0 (10.9)	1184.0 (10.9)	.001	897.7 (10.6)	922.0 (10.9)	.009	89.5 (1.5)	104.0 (1.7)	.019
Diabetes	1577.5 (14.8)	1600.0 (15.1)	.006	1173.5 (10.8)	1162.0 (10.7)	.003	779.5 (9.2)	789.0 (9.3)	.004	161.5 (2.6)	187.0 (3.1)	.025
Chronic kidney disease	331.5 (3.1)	319.0 (3.0)	.007	208.0 (1.9)	193.0 (1.8)	.010	107.0 (1.3)	97.0 (1.1)	.011	20.0 (0.3)	19.0 (0.3)	.003
Hypothyroidism	138.0 (1.3)	133.0 (1.3)	.004	106.5 (1.0)	110.0 (1.0)	.003	73.5 (0.9)	79.0 (0.9)	.007	19.5 (0.3)	24.0 (0.4)	.012
Parkinson's disease	606.0 (5.7)	696.0 (6.5)	.035	168.5 (1.6)	172.0 (1.6)	.003	181.0 (2.1)	191.0 (2.3)	.008	16.5 (0.3)	20.0 (0.3)	.010
Hepatic disease	356.5 (3.4)	369.0 (3.5)	.006	252.5 (2.3)	297.0 (2.7)	.026	218.5 (2.6)	217.0 (2.6)	.001	51.0 (0.8)	60.0 (1.0)	.016
COPD	651.0 (6.1)	637.0 (6.0)	.006	411.5 (3.8)	431.0 (4.0)	.009	265.0 (3.1)	303.0 (3.6)	.025	47.0 (0.8)	56.0 (0.9)	.016
Suicidal attempt	456.5 (4.3)	413.0 (3.9)	.021	439.5 (4.1)	440.0 (4.1)	<.001	408.0 (4.8)	384.0 (4.5)	.013	344.0 (5.6)	327.0 (5.3)	.012
Healthcare service use												
Inpatient admission, mean (SD)	1.48 (1.92)	1.44 (3.35)	.015	1.11 (1.49)	1.12 (2.38)	.008	1.05 (1.48)	1.03 (2.17)	.012	0.82 (1.47)	0.83 (1.97)	.004
Outpatient clinic appointment, mean (SD)	10.32 (18.62)	10.03 (11.81)	.019	7.51 (15.23)	7.90 (11.85)	.029	8.56 (16.05)	8.83 (12.41)	.019	5.11 (13.58)	5.32 (11.47)	.017
Emergency attendance, mean (SD)	1.81 (2.66)	1.77 (3.03)	.012	1.58 (2.72)	1.60 (2.59)	.006	1.76 (3.13)	1.75 (3.25)	.005	1.52 (2.83)	1.54 (2.64)	.008

112
113   SD, standardised difference; COPD, chronic obstructive pulmonary disease.
114   **eTable 7. Baseline Characteristics of Included Patients after Propensity Score Matching (Quetiapine, Risperidone, Sulpiride, and Trifluoperazine)**
115   **(continued)**

|	HR in matched cohort (95% CI)		
All-cause mortality	*Short-term*	*Mid-term*	*Long-term*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Chlorpromazine	**0·81 (0·71, 0·94)**	**0·76 (0·67, 0·86)**	**0·60 (0·55, 0·66)**
Aripiprazole	0·60 (0·19, 1·89)	**0·45 (0·20, 0·98)**	**0·42 (0·23, 0·76)**
Quetiapine	**0·36 (0·30, 0·44)**	**0·52 (0·46, 0·59)**	**0·72 (0·67, 0·77)**
Amisulpride	**0·33 (0·18, 0·64)**	**0·49 (0·33, 0·73)**	**0·75 (0·62, 0·91)**
Risperidone	**0·26 (0·20, 0·34)**	**0·57 (0·49, 0·66)**	**0·79 (0·73, 0·86)**
Olanzapine	**0·26 (0·09, 0·74)**	**0·31 (0·15, 0·67)**	**0·56 (0·38, 0·83)**
Trifluoperazine	**0·26 (0·14, 0·47)**	**0·34 (0·22, 0·52)**	**0·52 (0·41, 0·66)**
Sulpiride	**0·23 (0·16, 0·32)**	**0·52 (0·43, 0·63)**	**0·62 (0·56, 0·68)**
CVD mortality	*Short-term*	*Mid-term*	*Long-term*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Chlorpromazine	1·16 (0·85, 1·58)	0·86 (0·61, 1·23)	**0·59 (0·46, 0·74)**
Aripiprazole	1·15 (0·19, 7·03)	0·78 (0·07, 8·88)	0·55 (0·10, 3·06)
Sulpiride	0·59 (0·34, 1·03)	0·94 (0·62, 1·43)	0·78 (0·61, 1·00)
Quetiapine	**0·48 (0·31, 0·73)**	**0·62 (0·45, 0·87)**	**0·74 (0·61, 0·90)**
Trifluoperazine	0·46 (0·10, 2·18)	1·00 (0·31, 3·20)	0·48 (0·22, 1·05)
Risperidone	**0·38 (0·23, 0·65)**	0·98 (0·70, 1·36)	0·84 (0·68, 1·05)
Amisulpride	0·24 (0·05, 1·04)	0·97 (0·44, 2·12)	1·08 (0·67, 1·74)
Olanzapine	/	0·37 (0·04, 3·35)	1·05 (0·38, 2·92)
Pneumonia-related mortality	*Short-term*	*Mid-term*	*Long-term*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Chlorpromazine	**0·71 (0·52, 0·97)**	**0·66 (0·50, 0·87)**	**0·49 (0·42, 0·58)**
Amisulpride	0·58 (0·18, 1·80)	0·80 (0·40, 1·60)	0·83 (0·62, 1·11)
Quetiapine	**0·46 (0·33, 0·65)**	**0·63 (0·51, 0·78)**	**0·68 (0·60, 0·76)**
Risperidone	**0·33 (0·21, 0·52)**	**0·73 (0·56, 0·94)**	**0·84 (0·74, 0·96)**
Trifluoperazine	0·29 (0·07, 1·29)	**0·28 (0·08, 0·94)**	**0·42 (0·25, 0·72)**
Sulpiride	**0·22 (0·10, 0·45)**	0·73 (0·52, 1·03)	**0·63 (0·53, 0·74)**
Aripiprazole	/	0·94 (0·27, 3·24)	**0·28 (0·08, 0·98)**
Olanzapine	/	0·62 (0·20, 1·98)	0·94 (0·47, 1·89)

116 HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

117 **eTable 8. Mortality Risk by Duration of Effect in Matched Cohorts**

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	HR in matched cohort (95% CI)		
All-cause mortality	*Low dose*	*Moderate dose*	*High dose*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Chlorpromazine	**0·68 (0·64, 0·73)**	**0·50 (0·38, 0·65)**	0·74 (0·22, 2·48)
Risperidone	**0·66 (0·61, 0·71)**	**0·34 (0·19, 0·62)**	0·37 (0·10, 1·31)
Quetiapine	**0·61 (0·57, 0·65)**	**0·27 (0·15, 0·49)**	0·37 (0·08, 1·75)
Olanzapine	**0·49 (0·27, 0·89)**	**0·51 (0·32, 0·81)**	**0·09 (0·01, 0·65)**
Aripiprazole	**0·47 (0·28, 0·80)**	**0·17 (0·04, 0·72)**	1·41 (0·08, 25·57)
CVD mortality	*Low dose*	*Moderate dose*	*High dose*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Aripiprazole	0·84 (0·20, 3·57)	0·46 (0·05, 4·51)	/
Risperidone	**0·80 (0·67, 0·96)**	0·39 (0·08, 1·88)	/
Chlorpromazine	**0·77 (0·65, 0·92)**	0·56 (0·24, 1·29)	/
Quetiapine	**0·67 (0·57, 0·80)**	0·19 (0·02, 1·54)	/
Olanzapine	0·35 (0·04, 3·02)	0·73 (0·24, 2·22)	/
Pneumonia-related mortality	*Low dose*	*Moderate dose*	*High dose*
Haloperidol	1 (ref)	1 (ref)	1 (ref)
Olanzapine	1·52 (0·62, 3·69)	0·52 (0·20, 1·37)	/
Risperidone	**0·76 (0·68, 0·86)**	0·44 (0·14, 1·35)	0·24 (0·03, 2·11)
Quetiapine	**0·64 (0·58, 0·71)**	**0·27 (0·08, 0·95)**	/
Chlorpromazine	**0·57 (0·50, 0·66)**	**0·28 (0·14, 0·53)**	/
Aripiprazole	0·49 (0·18, 1·37)	/	/

119   HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

120   **eTable 9. Mortality Risk by Dosage Level in Matched Cohort**

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All-cause mortality	HR in matched cohort (95% CI)
Haloperidol	1 (ref)
Chlorpromazine	0·87 (0·72, 1·05)
Sulpiride	**0·46 (0·38, 0·56)**
Amisulpride	**0·48 (0·32, 0·71)**
Risperidone	**0·51 (0·44, 0·59)**
Quetiapine	**0·44 (0·38, 0·50)**
Olanzapine	0·51 (0·22, 1·14)
Aripiprazole	**0·38 (0·15, 0·95)**
Trifluoperazine	**0·34 (0·21, 0·54)**
CVD mortality	
Haloperidol	1 (ref)
Chlorpromazine	1·18 (0·75, 1·86)
Sulpiride	1·20 (0·81, 1·77)
Amisulpride	0·54 (0·22, 1·29)
Quetiapine	**0·56 (0·40, 0·78)**
Trifluoperazine	0·33 (0·07, 1·58)
Olanzapine	/
Aripiprazole	1·33 (0·22, 7·98)
Risperidone	**0·72 (0·52, 1·00)**
Pneumonia-related mortality	
Haloperidol	1 (ref)
Chlorpromazine	0·88 (0·55, 1·40)
Sulpiride	**0·48 (0·33, 0·72)**
Amisulpride	0·79 (0·42, 1·48)
Risperidone	**0·67 (0·53, 0·86)**
Trifluoperazine	0·43 (0·17, 1·09)
Olanzapine	1·41 (0·35, 5·77)
Aripiprazole	0·62 (0·15, 2·51)
Quetiapine	**0·44 (0·35, 0·55)**

122   HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

123   **eTable 10. Mortality Risk with Observation Period Censored at Prescription End**

124
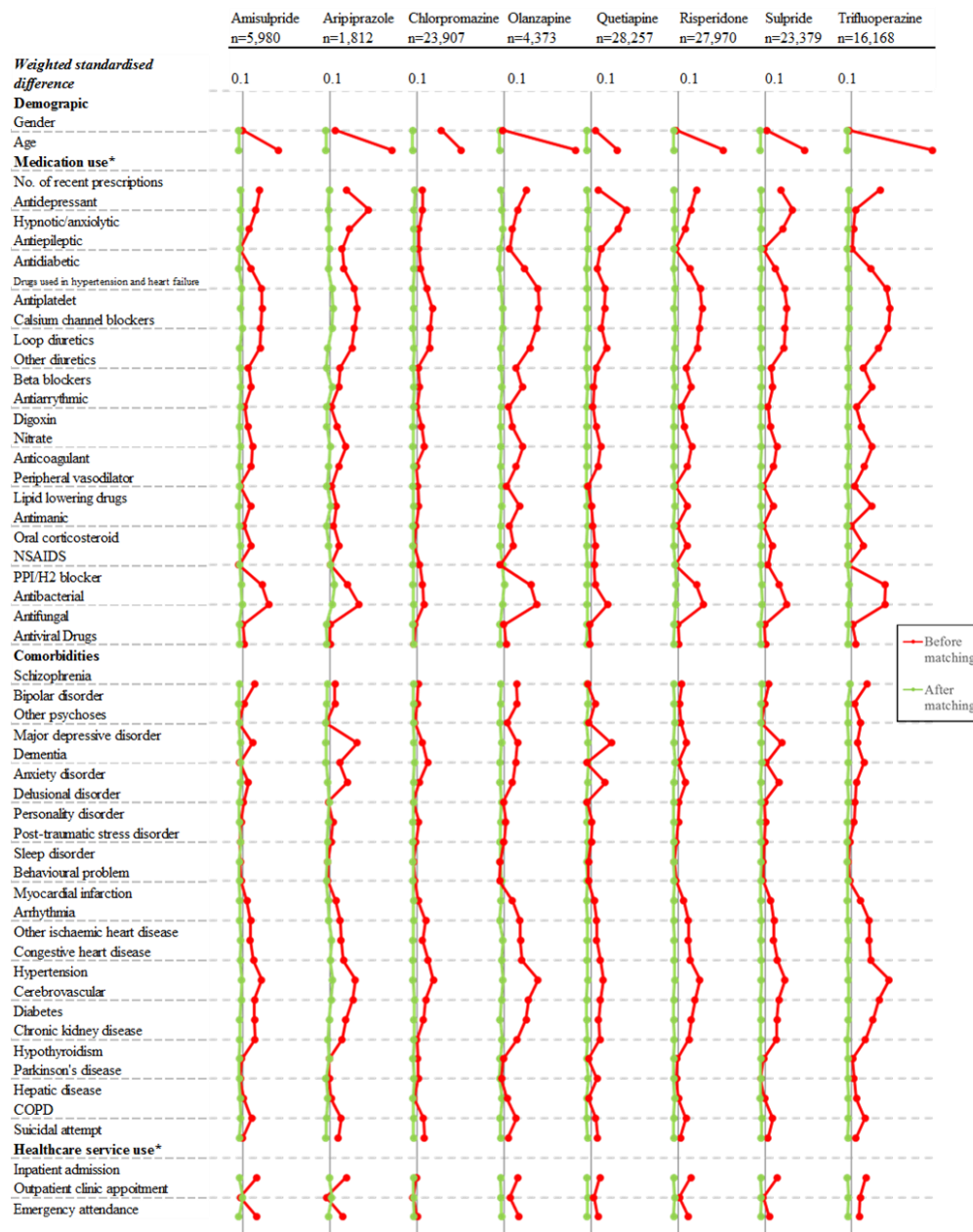
*Medication use or healthcare service use in the 365 days before index date.

NSAIDS, non-steroid anti-inflammation drugs; PPI, proton pump inhibitor; H2 blocker, histamine-2 receptor

blocker; COPD, chronic obstructive pulmonary disease.

eFigure 1. Weighted Standardised Difference of Covariates between Haloperidol and Individual Other Drugs Before and After Matching
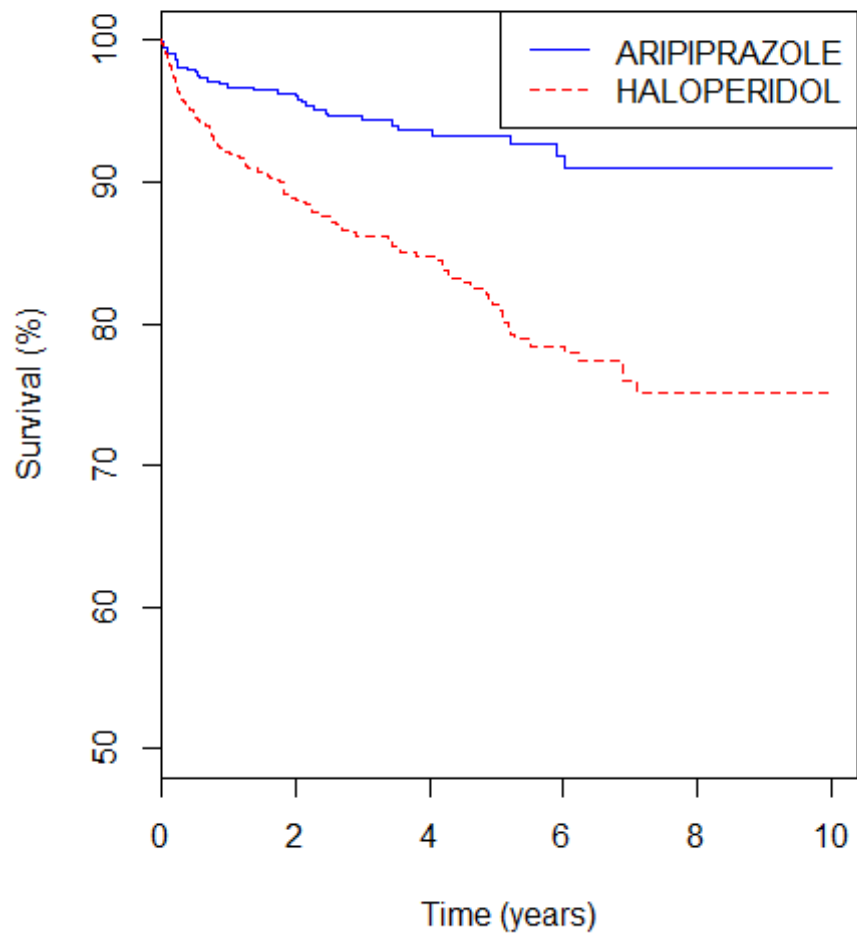
Version Date: 20191113

130
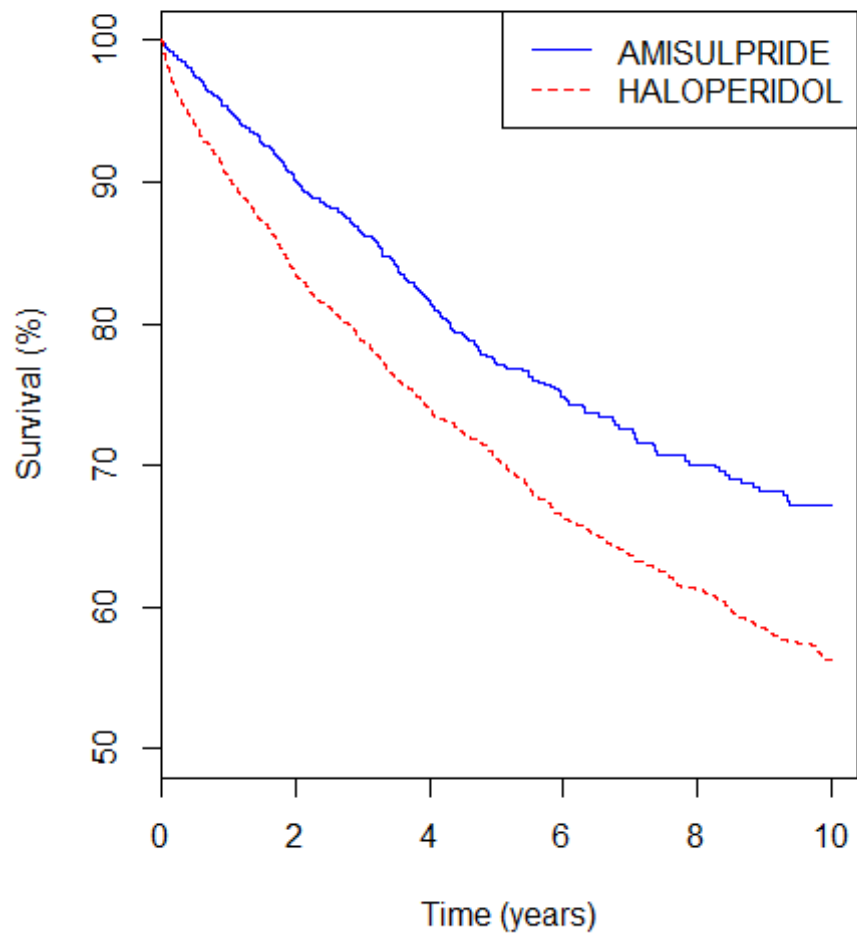
eFigure 2. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Amisulpride versus

Haloperidol Matching by Propensity Score

133

134   **eFigure 3. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Aripiprazole versus**

135   **Haloperidol Matching by Propensity Score**
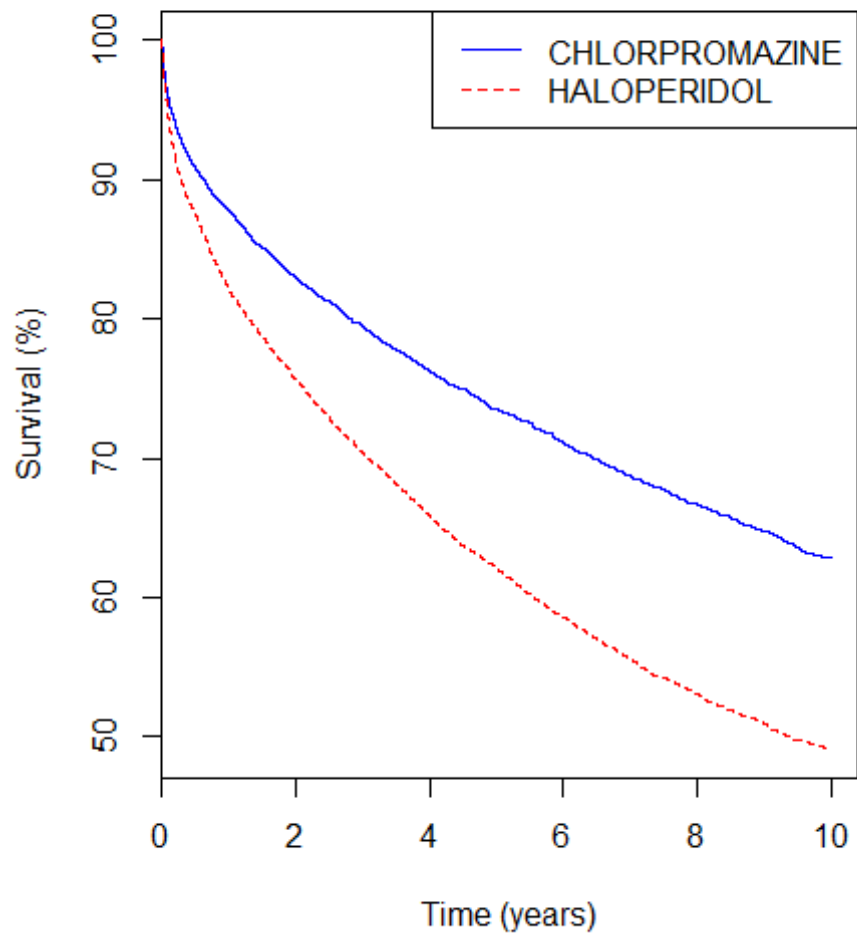
136

137 **eFigure 4. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Chlorpromazine versus**
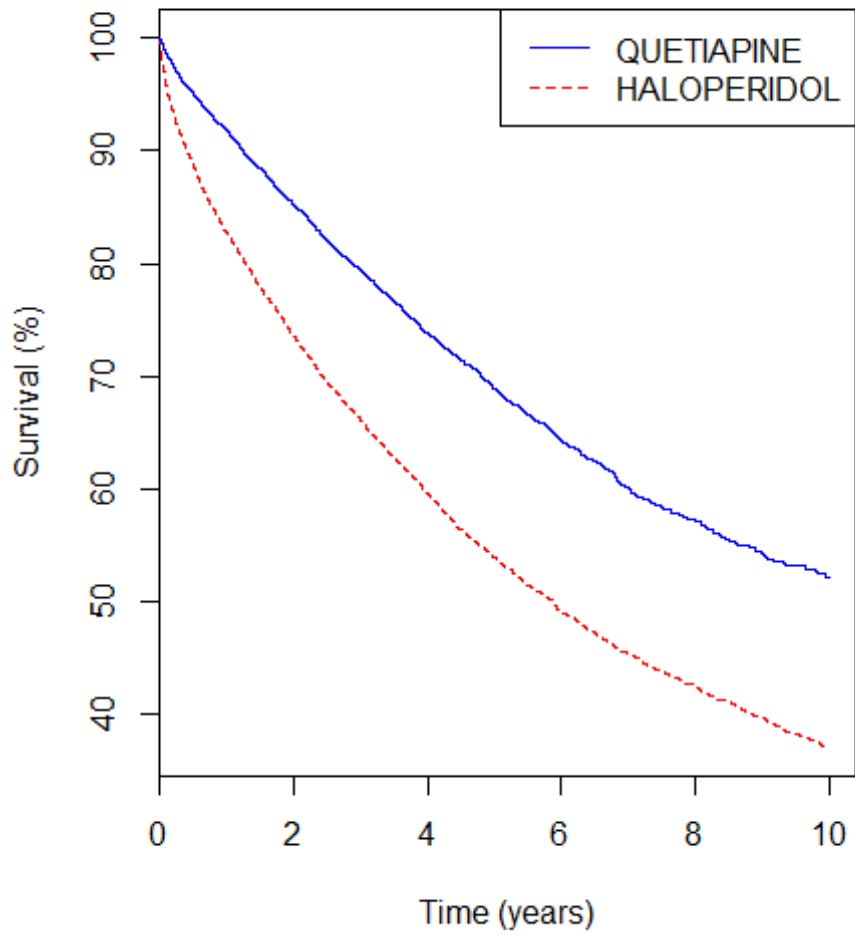
138 **Haloperidol Matching by Propensity Score**

139
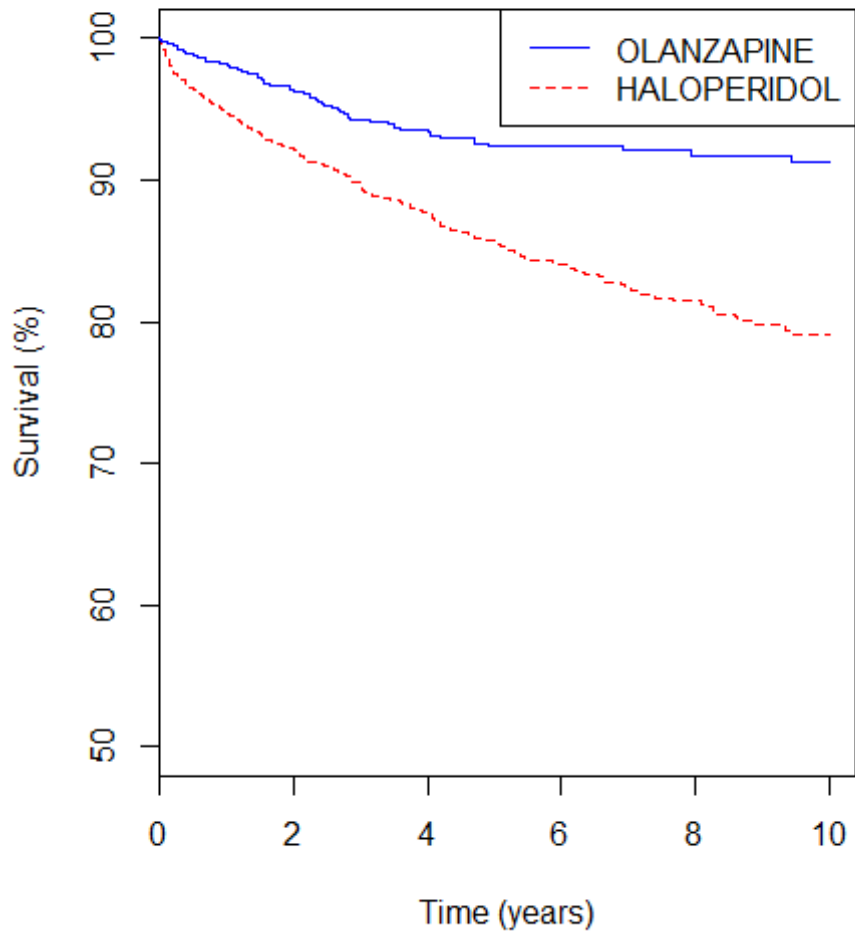
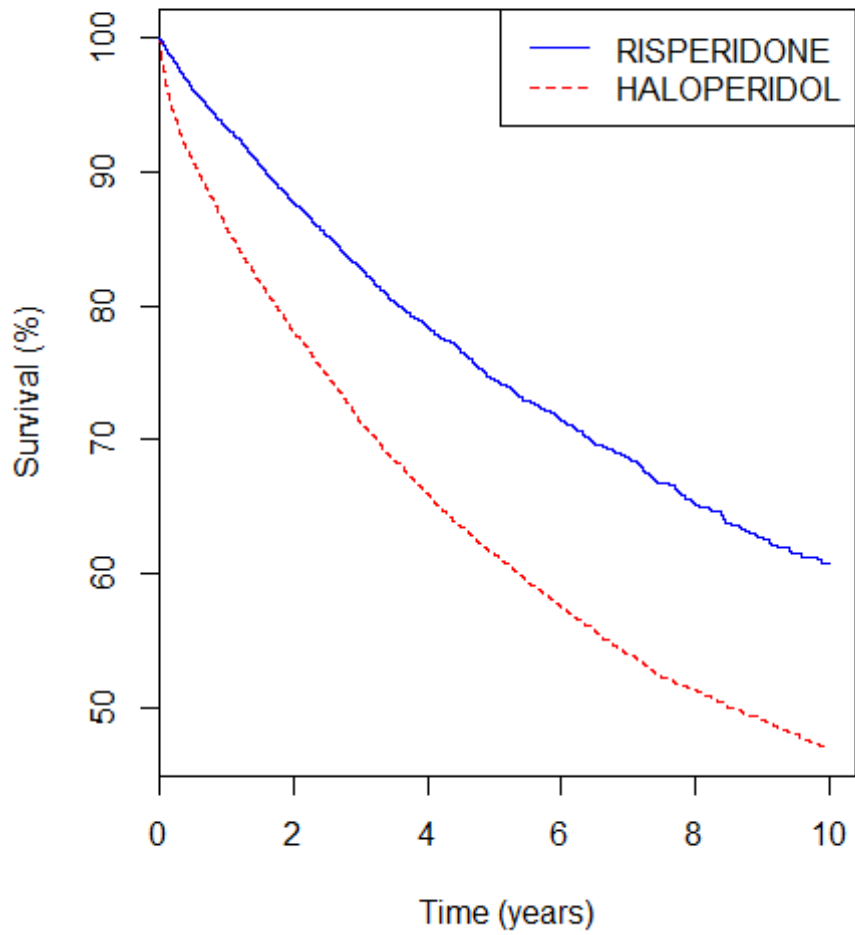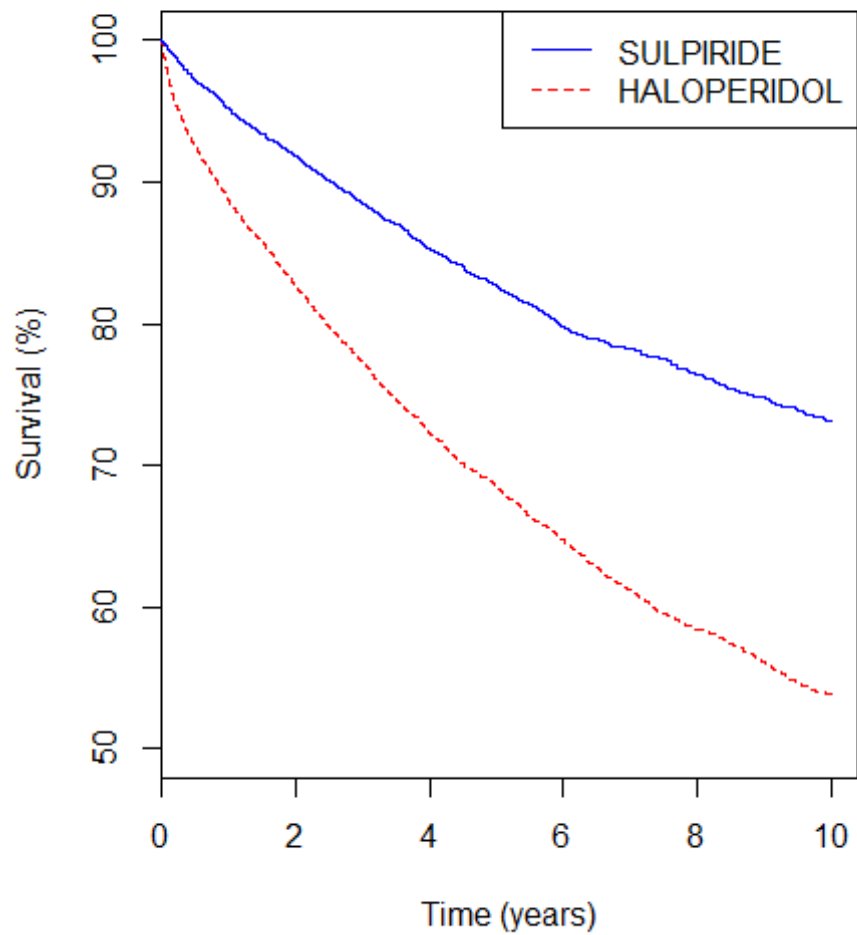**eFigure 5. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Olanzapine versus**

Haloperidol Matching by Propensity Score

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143   **eFigure 6. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Quetiapine versus**

144   **Haloperidol Matching by Propensity Score**

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146   **eFigure 7. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Risperidone versus**

147   **Haloperidol Matching by Propensity Score**

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149   **eFigure 8. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Sulpiride versus**

150   **Haloperidol Matching by Propensity Score**

151

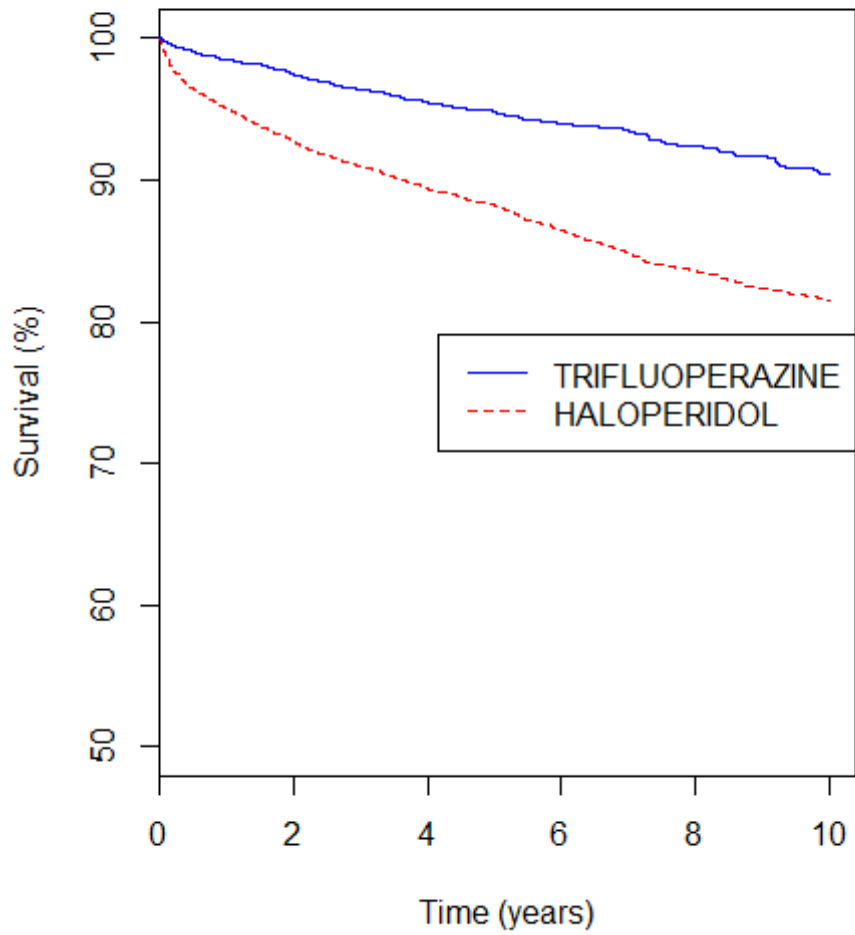**eFigure 9. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed Trifluoperazine versus**

Haloperidol Matching by Propensity Score