Data Supplement for Wimberley et al., Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia. Am J Psychiatry (doi: 10.1176/appi.ajp.2017.16091097)

Supplementary Material

Table S1 Definition of treatment periods based on registry data.

	Operational definitions
Estimated duration of a single prescription	Median time interval between prescription redemption dates calculated within individuals and type of antipsychotic medication (defined by Anatomic Therapeutic Classification (ATC) groups) for patients with at least four redemptions within ATC group. If either the patient has less than four redemptions within a given antipsychotic medication type or if the estimated prescription duration exceeds the number of defined daily doses by 100 days, the prescription duration will be estimated by the median time interval between prescription redemptions within type of antipsychotic medication based on all individuals in the cohort.
Grace period/maximum allowed gap	100% of the estimated duration of the specific prescription.
Start and end of a treatment period	Start = date of first redemption or first redemption occurring after gap exceeded grace period. End = date of last redemption of subsequent redemptions of the same ATC (redeemed within estimated duration plus grace period) plus estimated duration of the last prescription.
Monotherapy	Periods with use of one single type of antipsychotic medication.
Polypharmacy	Overlapping periods of concurrent treatment with two or more different antipsychotics.

Table S2 Hazard ratios and 95% CIs presented for all-cause death and self-harm for different categorizations of time-dependent antipsychotic (AP) treatment with long-acting injectable (LAI) antipsychotics[a] as a separate exposure category.

N=2370				Model A Crude		Model B Adjusted[b]		Model C Adjusted[c]	
Time-dependent treatment	Events/ total person-years	Rate per 100 person-years	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
All-cause death									
N(events)=158									
Clozapine (ref)	32/5345	0.60	0.42-0.85	1		1		1	
LAI AP	20/1661	1.20	0.78-1.87	2.05	1.17-3.59	1.66	0.94-2.93	1.28	0.72-2.26
Other AP	46/5568	0.83	0.62-1.10	1.38	0.88-2.17	1.33	0.85-2.10	1.14	0.72-1.79
No AP	60/4233	1.42	1.10-1.83	2.42	1.57-3.72	2.45	1.59-3.77	1.99	1.28-3.08
Self-harm									
N(events)=602									
Clozapine (ref)	137/4677	2.93	2.48-3.46	1		1		1	
LAI AP	69/1129	6.11	4.83-7.74	2.19	1.64-2.92	1.90	1.42-2.53	1.24	0.99-1.79
Other AP	254/4261	5.96	5.27-6.74	2.13	1.73-2.63	2.08	1.69-2.56	1.51	1.22-1.87
No AP	142/3093	4.59	3.89-5.41	1.72	1.36-2.17	1.65	1.30-2.09	1.23	0.97-1.56

[a] Long-acting injectables were identified based on product numbers which unambiguously identify licensed drugs in Denmark.

[b] Adjusted for sex, and time-dependent covariates: age, calendar year, prior episodes of self-harm, substance abuse, and comorbid somatic disorders.

[c] Including adjustment for psychiatric hospitalization within previous year.

Initial-treatment approach

We defined treatment according to an initial treatment carried forward approach, i.e. clozapine versus non-clozapine antipsychotics at baseline (time point of meeting register-based criteria for treatment-resistant schizophrenia). Individuals initiating clozapine at baseline or within a three-month treatment exposure window after baseline were assigned to the initial clozapine-treated group. This approach allowed for including a larger set of potential confounders by applying propensity score matching. Follow-up started at first clozapine redemption or three months after meeting criteria (ii) for treatment-resistant schizophrenia, whichever came first, which resulted in an initial-treatment cohort after exclusion of 18 individuals from the original study cohort. A propensity score was estimated for each individual in a logistic regression model including all variables listed in Supplementary Table 2. Cubic splines (with four knots) for age and calendar year were included. We did 1:1 propensity score matching without replacement within levels of sex and age ranges and within a pre-specified caliper width. Multivariable Cox regression analyses on the initial-treatment cohort as well as analysis on propensity score-matched cohort were performed.

Initial treatment groups resulted in 1298 (55.2%) initial clozapine users and 1054 (44.8%) initial non-clozapine users. The register-based definition of treatment-resistant schizophrenia delineated a relatively homogeneous subgroup of individuals with schizophrenia with treatment groups being equally distributed across several baseline characteristics (Supplementary Table 2) and with a substantial overlap in propensity score distributions (Supplementary Figure 1). Still, the discrimination was fair (Harrell's C statistic=0.65), and the resulting propensity score-matched cohort was balanced across all baseline characteristics (Supplementary Table 2).

When comparing rates in initial non-clozapine users with initial clozapine users in a propensity score-matched cohort with no restrictions of follow-up, no difference was observed, HR = 1.00 (0.70 – 1.45) (Supplementary Table 3, Model 3). Crude and adjusted analyses including the initial-treatment exposure, based on the initial-treatment cohort before propensity-score matching, resulted in similar results (Supplementary Table 3, Model 1 and 2).

When comparing rates in initial non-clozapine users with initial clozapine users in a propensity score-matched cohort, we found a significantly increased rate of self-harm, adjusted HR = 1.73 (1.42 – 2.11). This association was statistically significant in all models (Supplementary Table 3).

When restricting the initial-treatment analysis to one year of follow-up, the rate was two-fold increased, HR = 2.02 (0.61 – 6.67) in non-clozapine users, indicating a decreased mortality in the first year after clozapine initiation. However, the confidence intervals were wide due to a

relatively small number of deaths (n = 15) in the first year of follow-up (Supplementary Table 3, Model 4).

Table S3 Baseline characteristics in the initial-treatment cohort and propensity score-matched cohort across groups of initial treatment.

		Initial-treatment cohort (N=2352)		**Propensity score-matched cohort** (N=1728)	
	All	**Clozapine**	**Non-clozapine**	**Clozapine**	**Non-clozapine**
	N=2352	N=1298 (55.2%)	N=1054 (44.8%)	N=864 (50%)	N=864 (50%)
Baseline factors	%	%	%	%	%
Age < 30	49.2	50.2	48.0	49.1	49.1
Sex (female)	45.7	44.1	47.8	54.2	54.2
Marital status (living alone)	80.8	83.3	77.8	80.1	79.9
Psychiatric hospitalization in previous year	63.6	66.3	60.2	60.8	63.4
Substance abuse	44.7	42.7	47.2	47.9	47.5
Drugs redeemed in previous year					
Antidepressants	49.9	44.2	56.8	57.2	54.3
Benzodiazepines	57.8	52.0	65.0	65.7	61.7
Non-neuroleptic drugs	63.9	58.4	70.8	73.0	69.0
Number of episodes of self-harm					
0	59.4	60.2	58.3	55.8	57.1
1	14.2	13.9	14.6	15.3	15.2
2-4	15.5	14.3	16.9	17.7	16.8
5+	11.0	11.6	10.2	11.2	11.0
Psychiatric comorbidity					
Schizo-affective disorder	9.8	10.9	8.4	8.3	9.7
Other schizophrenia spectrum disorder	59.5	59.9	58.9	58.7	60.0
Depression	31.9	30.2	34.1	33.9	33.6
Personality disorder	43.2	41.7	45.2	44.9	43.5
Somatic comorbidity (Charlson score>0)	16.6	16.2	17.2	18.2	18.9
Education (primary only)	61.8	62.3	61.2	62.8	62.2
Working status					
In work	11.6	10.7	12.6	11.7	11.5
outside working force	35.7	34.6	37.1	35.6	34.7
early disability benefit	52.7	54.7	50.3	52.7	53.8
Urbanicity (capital area)	22.5	22.6	22.4	22.3	21.9
Family history of schizophrenia					
Yes	8.9	9.5	8.2	8.4	8.3
No	88.0	87.8	88.2	88.2	88.4
Unknown	3.1	2.8	3.6	3.4	3.2

Data Supplement for Wimberley et al., Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia. Am J Psychiatry (doi: 10.1176/appi.ajp.2017.16091097)

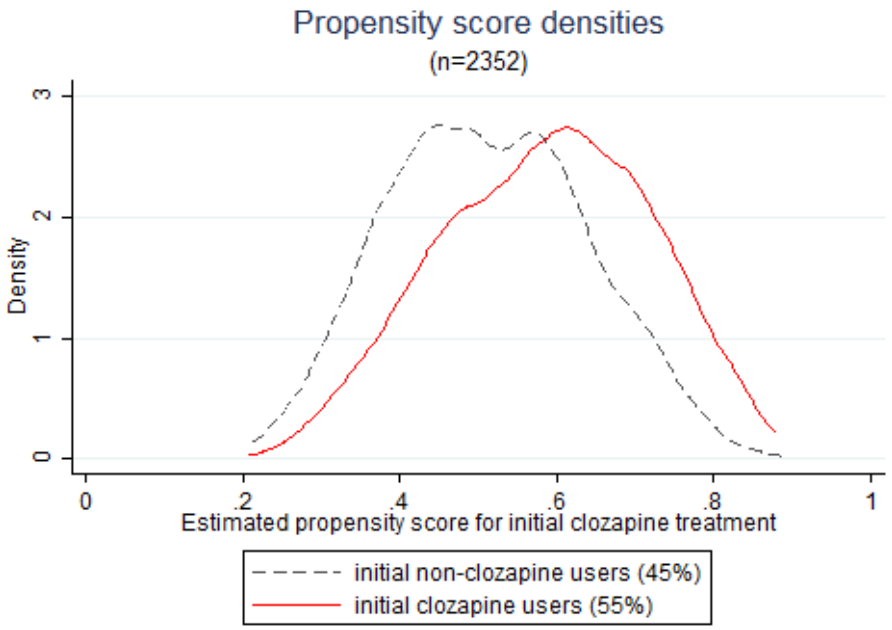

Figure S1 Distributions in the original initial-treatment cohort of the propensity score for clozapine treatment in initial clozapine users versus initial non-clozapine users, all meeting criteria for treatment-resistant schizophrenia.

Table S4 Hazard ratios and 95% CIs presented for all-cause mortality and self-harm for comparing initial non-clozapine antipsychotic (AP) users with initial clozapine users.

N=2353				**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	Events/ total person-years	Rate per 100 person-years		Crude		Adjusted[a]		PS-matched cohort[b]		Restricted to one-year follow-up[c]	
Initial-treatment			95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
All-cause death											
N(events)=154											
Clozapine	87/9582	0.91	0.74-1.12	1		1		1		1	
Non-clozapine AP	67/6955	0.96	0.76-1.22	1.06	0.77-1.46	1.02	0.73-1.43	1.00	0.70-1.45	2.02	0.61-6.67
Self-harm											
N(events)=584											
Clozapine users	282/7873	3.58	3.19-4.03	1		1		1		1	
Non-clozapine AP	302/5152	5.86	5.24-6.56	1.64	1.39-1.94	1.87	1.57-2.23	1.73	1.42-2.11	1.94	1.40-2.70

[a] Adjusted for sex, age, calendar year, substance abuse, psychiatric hospitalization in the previous year, prior episodes of self-harm, somatic diagnoses, psychiatric diagnoses, primary education, living in the capital area, time since first SZ (< 2 years), calendar year at baseline (4 lev).

[b] Analysis based on a 1:1 propensity score-matched cohort, levels of sex and age (18-25, 25-30, 30-35, 35+ years). N=1711. N(deaths)=118 and N(self-harm)=435.

[c] N(deaths)=15 and N(self-harm)=196.