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TITLE

Clozapine treatment and offending: a within-subject study of patients with psychotic disorders in Sweden

RUNNING TITLE

Clozapine treatment and offending

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ABSTRACT:

Clozapine treatment may have beneficial effects on behavioural outcomes in psychotic disorders, including violent offending. Although clozapine and other antipsychotics have been linked to lower levels of violent behaviour, these have been primarily in small selected samples, and population-based estimates have been limited and imprecise.

We aimed to assess the effect of clozapine treatment on the rate of violent and non-violent offending. We carried out a within-person mirror image study of the Swedish population based on linked prescription, hospitalization, and sociodemographic registers. Outcomes were violent, non-violent, and overall offences occurring before and after clozapine, or olanzapine, initiation. Comparison of effects of clozapine and olanzapine on key variables was modelled with interaction terms. We found that periods of mirror image observation time ~~of~~ with clozapine treatment were associated with a much lower rate of violent offending compared to periods before treatment (rate ratio (RR)=0.13(95% confidence interval (CI): 0.05, 0.34). Reductions in non-violent offences were smaller in magnitude (RR: 0.37, 95%CI: 0.17, 0.80). There was a statistically greater rate reduction effect on violent offences for clozapine, than olanzapine (rate ratio for interaction=4.84, 95%CI: 1.56, 14.86, p=0.002). ~~Statistically greater rate reductions for violent offences for clozapine compared to olanzapine were noted in those with admission for any substance use disorder, including those with alcohol use- and cannabis use- disorders.~~ In patients with psychotic disorders, clozapine treatment is associated with a lower rate of violent offending compared to olanzapine. ~~Clozapine may reduce offending through direct effects on psychotic symptoms, or indirectly through lifestyle changes, including use of drugs or alcohol.~~

INTRODUCTION

Clinical management of psychotic disorders typically involves a combination of psychological and pharmacological therapy, with the aim of eliminating or limiting symptoms and optimizing functioning[1]. However, violent offending is also an important adverse outcome in psychotic disorders[2], and is more common in patients diagnosed with psychotic disorders compared to the general population[3]. ~~Psychotic~~ Patients with psychotic disorders ~~patients~~ are ~~frequently~~ often ~~inconsistently~~ intermittently treated[4], and studies suggest violence is higher in untreated patients[5].

Some studies have reported lower levels of violence in people treated with antipsychotics, particularly second generation drugs[6, 7], and especially clozapine[8, 9]. Such observations are complicated by the strong possibility of confounding by indication[10]. Firstly, a violent episode may trigger a psychiatric evaluation, and the initiation of treatment. Secondly, given that clozapine requires a commitment by the patient to accept oral medication and frequent blood tests, it may be that people who are prescribed clozapine are systematically different from those prescribed other treatments in ways that mean that the simple comparison of violence occurrence between groups may not be valid.

Accumulating evidence continues to support the clinical effectiveness of clozapine on symptoms and hospital use in treatment refractory schizophrenia[11, 12]. National registers linked to prescribing information have clarified the real world effectiveness of antipsychotic drugs for a range of outcomes[13, 14]. However, identifying convictions for violent behaviour from national registers is not straightforward. A single conviction may refer to a mixture of separate constituent offences, some of which may be violent, and others non-violent; for example, a person may be convicted for a combination of theft, assault, and a drug-related offence. Fazel[15] reported that antipsychotic treatment reduced violent convictions (i.e. convictions for offences where at least one offence was violent) in a Swedish population cohort, comparing periods of time on treatment with time off treatment, over a three-year period. Effect estimates

for clozapine were under-powered in the Fazel study to investigate clozapine, and focused on

In this paper, we address these issues by (a) considering occurrence of violent offending in people treated for psychotic disorders with clozapine, comparing equal time periods before initiation with periods of time after, (b) test whether any effect of clozapine on violent offending is greater than that expected of a general antipsychotic effect, by comparing the effect of clozapine to that of olanzapine, the most commonly prescribed antipsychotic drug in Sweden, and (c) assessing violent and non-violent offences separately. We draw upon registry data on clozapine and olanzapine prescriptions in Sweden, linking it with national data on convictions to identify violence-related outcomes. Our analysis is within-subject i.e. all comparisons made are of offending before initiation compared to after initiation within patients.

METHODS

Using a within-subject design, also known as a mirror-image model, we compared the rate of offences during treatment with clozapine or olanzapine with periods of time of equal duration before prior to the initiation of that treatment.

Data sources

The unique Swedish personal identity number[21] was used to link information from the following population-based registers:

1. The Causes of Death Register, comprising information on all deaths of Swedish residents since 1952 with causes of death coded according to the International Classification of Diseases (ICD)[22],
2. The National Patient Register (NPR), including all individuals admitted to psychiatric or general hospitals, with complete coverage for all in-patient care since 1987, and for ~~specialized~~ hospital-based (as opposed to primary care-based) out-patient care since 2006[23],
3. The Total Population Register, containing comprehensive information on age, sex, place of residence, and other relevant demographic characteristics[24] on Swedish people,
4. The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), which integrates existing data from the labour market, educational and social sectors[25],
5. The Register of Court Conviction, containing information on all court convictions and offences in Sweden for individuals 15 years of age or older since 1973[26], and
6. Lastly, the Prescribed Drug Register[27], which contains patient identities for all dispensed prescribed drugs to the entire Swedish population since July 1st 2005, classified using the five-level anatomical therapeutic and chemical classification system (ATC).

Derivation of study population

All prescriptions for clozapine and olanzapine (ATC-code N05AH02 and ATC-code N05AH03 respectively) registered from July 2005 until June 2012 were retrieved, excluding individuals who were prescribed both medicines, either concurrently or at different points in this period. Those that had a start date during 2005 were excluded, as a conservative measure to ensure the only new initiations of clozapine treatment were included. Of these, all Swedish people born 1955-1988 who had a first prescription of clozapine or olanzapine between January 1, 2006 and December 31, 2010 were kept. Those without a psychotic disorder or schizoaffective disorder (ICD-10 F20-F29) were further excluded (257 people).

In order to be confident that individuals included in the analysis were exposed to sustained periods of treatment, we limited our study to individuals treated with each drug for a minimum of 8 weeks. We identified 1176 people living in Sweden who were initiated on clozapine during the study period, and 4527 who were initiated on olanzapine. Among those prescribed clozapine, 1126 received more than one prescription of clozapine, of which 1086 had complete information on observation time (40 had missing data on the end of observation time, as defined below), of which 1004 were treated with clozapine for longer than 8 weeks and were included in the analysis. Among those prescribed olanzapine, 3967 had more than one olanzapine prescription, of which 3238 had ~~valid~~ complete information on observation times (729 had missing data on the end of observation time, as defined below), of which 2258 were continuously treated for 8 weeks or longer. Thus, our analysis was based on 1004 subjects treated with clozapine and 2258 subjects treated with olanzapine. To evaluate any influence of the 8 weeks criterion on our results, we inspected data on individuals prescribed each drug for less than 8 weeks.

Definition of observation time in subjects:

Data on convictions were collected for individuals in the study population described above, for (a) as long as possible following initiation of the drug, and (b) for a period of time *of equal duration prior* to the initiation of the drug.

Firstly, the "forward" observation time at risk for these outcomes was defined, using the Total Population register, as the elapsed number of days from the date of initiation of the drug to either:

1. the discontinuation date for the drug (defined as the last date of prescribed medication where this occurred prior to a period of 6 months without a prescription for the drug, or without an inpatient psychiatric admission during this period), or
2. date of emigration, or
3. date of death, or
4. date of the end of the study period, which was 31st December 2011.

Secondly, having identified the forward observation time at risk, a backward observation time was defined for each subject of the same length. In the event that the backward observation time extended to a point before the start of the prescription register, the forward observation time was shortened to match the backward observation time. Data on offences were then gathered, classified by whether they occurred in the "before" period (prior to initiation of the drug) or the "after" period (during drug treatment), within the mirror image observation time.

Measurement of outcomes

Dates of all offences for which there were convictions during the mirror image observation time (1st January 2006 – 31st December 2011) were collected for all study participants. We classified offences into violent offences and non-violent offences. Violent offences included manslaughter, homicide, assault, gross assault, assault on a public official, arson, murder, unlawful threat, sexual crimes, crimes involving a weapon, cruelty to an animal, and infanticide. A full list of offences, and their classification into 'violent' and 'non-violent', is

displayed in table 1. Counts for violent and non-violent offences, and overall offences, were generated based on this information.

Measurement of covariates

Owing to the within-subject design, account was taken of characteristics that did not change over time: data on these were available for gender, age, highest educational attainment (categorized into compulsory education (≤9 years), "high school" education (10- 12 years), and University or higher (≥13 years)), born in Sweden, the age and year of psychotic disorders diagnosis, and the age and date of drug initiation. We also considered characteristics that changed over time: employment status, presence of salary (as a binary variable yes/no), social salary (salary derived from social benefits, in quintiles), living in one of top three biggest cities (Stockholm, Gothenburg or Malmö), and the presence of unemployment benefit (a state benefit specifically for unemployment). This information was available 2 years before drug start, and at the time of drug start, and was used to measure characteristics in the before and during observation periods within the mirror image observation time, respectively. ~~To examine the effect of clozapine on offending in individuals with psychotic disorders comorbid with other mental and behavioral disorders, information from the National Patient Register was used to classify eligible subjects by whether they had one or more admissions at any time for the following reasons: any substance-use disorder, alcohol-use disorder, cannabis-use disorder, and sedative-use disorder. The substance use disorder category was inclusive of admissions for alcohol (ICD-10 code: F10, ICD-9: 303, 305A, 291A-291X, ICD-8: 291, 303), cannabis (ICD-10: F12 except for F12.5 and F12.7, ICD-9:-304D, ICD-8: 304.50), sedatives (ICD-10:-F13, ICD-9: 304B, ICD-8: 304.20, 304.30), stimulants (ICD-10: F14, F15, ICD-9: 304C, 304E, ICD-8: 304.40, 304.60), and opiates (ICD-10:-F11, ICD-9: 304A, ICD-8: 304.00, 304.10). Information on other mental disorders was based on admission diagnoses for mood disorder (ICD-8:296.0, 296.1-296.9; ICD-9: 296.00-296.16, 311; ICD-10: F30-F39), and anxiety disorders(ICD-8: 300.0-300.9; ICD-9: 300 except 300E, 308-309, 306, 307W; ICD-10:F40-F48).~~

Analysis

All analyses were performed in Stata 14[28]. ~~Sociodemographic characteristics and substance-related and other comorbidities were described for both drugs and compared using chi-squared tests.~~ Offence rates were expressed per 100 persons. Owing to large numbers of zeroes (i.e. observation periods where no offences occurred), poisson, zero-inflated poisson, and zero-inflated binomial regression models were compared on fit, assessed by both the Akaike Information Criteria (AIC) and the Bayes Information Criteria (BIC). Zero-inflated negative binomial regression models gave best fit, and this model framework, incorporating robust standard errors, was retained. Counts of violent, non-violent, and overall offences were compared by estimating the main effect (rate ratio) of treatment status with clozapine/olanzapine, comparing offence rate before treatment with during treatment. Difference in violence-reducing effects between clozapine and olanzapine were estimated by including an interaction term for drug (clozapine vs. olanzapine). All covariates were entered into zero-inflated negative binomial regression models in order to arrive at an adjusted estimate. Given the within-subject design, only time-changing covariates, namely employment status, income, residing in one of Sweden's three biggest cities, and unemployment benefit receipt were evaluated as potential confounders, by deriving and adjusting for categorical indicators for the before and the during observation period within the mirror image observation time. Age and calendar year at drug initiation/psychotic disorders diagnosis, gender, highest educational attainment, and whether the person was born in Sweden were not included as covariates because they did not vary within subjects. ~~Effects were estimated stratified by these variables, and by the presence of admissions for substance use disorders (comprising alcohol use-, cannabis use-, sedative use-, stimulant use-, and opiate use-related disorders), and the presence of any admissions for mood disorder or anxiety disorder.~~

Zero-inflated negative binomial models are estimated in two parts[29], consisting of a negative binomial model, in this study estimating counts of violent offences in patients who offend, which was the focus of our analysis. Zero-inflated negative binomial models also estimate a logit model, predicting excess zeros, in this study, zeros refer to periods of observation within

the mirror image observation time without offences, and we included inflation coefficients for age and gender, reflecting that these were the main influences on zero-offending[30]. The negative binomial model also estimates a dispersion parameter, quantifying the extent to which variance exceeds that expected under a poisson model. Supplementary analyses tested crude and fully adjusted associations stratified by gender (tables S4 and S5), and by mirror image observation time, dichotomized at 3 years (tables S6 and S7).

RESULTS

Table 1 describes the coding of offences into violent and non-violent categories used for this study. Table 2 summarises sample characteristics. A total of 2258 people treated with olanzapine met criteria for the study, of which 1385 (61.3%) were male, compared to a slightly greater proportion in clozapine-treated patients (66.0%, n=1004). More than three-quarters of the olanzapine patients were born in Sweden (76.2%), compared to nearly 80% of the clozapine group. Treatment for two years or more was more common among clozapine subjects than olanzapine (51.4% compared to 31.9%). ~~The prevalence of any admissions for substance use disorders was similar between subjects treated with clozapine and with olanzapine (clozapine: 32.7%, olanzapine: 32.9%), with similarities in proportion of specific substance use disorders between the two groups.~~ Any admission for mood disorder was also commoner in the olanzapine group (36.5%, compared to 32.0% in the clozapine group). Between treatment groups, there was difference in duration of observation time, with a higher proportion of olanzapine patients treated for less than a year, and a higher proportion of clozapine patients (about a third) treated for more than three years compared to the olanzapine group (around a fifth). There was statistical evidence for differences between clozapine and olanzapine treated groups for all covariates included in this study.

Table 3 summarises data on offences. Based on 369 offences in the clozapine group, and 960 offences in the olanzapine group, we estimated a rate reduction of around 75% in the clozapine group, and 50% in the olanzapine group with statistical evidence of difference between the two drugs (p value for interaction between drug and period of observation=0.015). The rate reduction for non-violent offences, comparing before treatment to during treatment for clozapine, was 63% after adjustments, compared to 39% for olanzapine. For violent offences, the fully adjusted rate reduction for treatment compared to before treatment was 87% for clozapine, and 8% for olanzapine (RR for clozapine: 0.13, 95%CI: 0.05, 0.34, RR for olanzapine: 0.82,95%CI:0.47, 1.43, p value for the interaction between drug and period of ~~treatment~~observation: 0.002). In the final adjusted model for overall offences, female gender (compared to male gender) predicted zero offences during periods of observation (p=0.027), but age did not, and neither gender nor age were statistically evidenced predictors of zero counts for non-violent, or overall offences.

~~Statistical evidence for clozapine effects on violent offending were evident on stratification for all selected comorbidities, with the exception of those with a history of sedative- , stimulant-, and opiate-use disorders(table 4). Violent offences rate reductions for olanzapine were generally lesser in magnitude, with statistical evidence for interaction between drug and period of treatment for substance-use disorders, alcohol use disorders, and cannabis use disorders. Clozapine treatment was associated with reduced violent offending rate for those with any substance use-related disorder (RR:0.07, 95%CI:0.02,0.24), alcohol use disorder (RR:0.09, 95%CI:0.02,0.37), cannabis use disorder (RR:0.10, 95%CI: 0.01,0.73), mood disorder (RR: 0.36, 95%CI: 0.13,0.99), and anxiety disorder (RR: 0.13, 95%CI: 0.04,0.46), with olanzapine associated with reductions in violent offence rate only for those with overall substance use disorder (RR: 0.40, 95%CI: 0.19,0.87). For non violent offences, clozapine treatment was associated with reduced offence rate in those with opiate use disorder (RR:0.05, 95%CI: 0.01, 0.64), and olanzapine was associated with non-violence offence rate reductions in those with any substance use disorder (RR:0.58, 95%CI: 0.40,0.83) and alcohol use disorder only (RR: 0.60, 95%CI: 0.38,0.96). Both clozapine and olanzapine were was~~

Time-varying characteristics for olanzapine-treated and clozapine-treated subjects are shown in table S1 of the supplementary material. The proportion of people working fell slightly for subjects treated with both drugs. The presence of salary fell among both the olanzapine group (22.7% to 17.8%) and the clozapine group (15.8% to 9.7%). Model estimates from the zero prediction part of final models for violent, non-violent and overall offences are displayed in table S2 of the Supplementary Material. ~~. Interaction terms from models based on patients with comorbidities, and zero-prediction coefficients and dispersion parameters for these models, are displayed in table S3.~~ In this paper, final estimates for the effects of clozapine and olanzapine on offending, interaction terms and interaction p values are presented in table 3. ~~Effect estimates and interaction p values for models based only on those with comorbidities are presented in table 4.~~ Zero-prediction coefficients and dispersion parameters for violent, non-violent and overall offences are presented in table S2. ~~, and table S3 displays interaction terms for each comorbidity, and zero-prediction coefficients and dispersion parameters for each model.~~ Estimates restricted by gender gave similar results, however among women, statistical evidence was insufficient at the 5% alpha level (table S4). Rate reductions were less among those with a mirror image observation time of shorter than 3 years (table S5), compared to those with a mirror image observation time of greater than 3 years (table S6). No violent offences were identified among 190 subjects who were prescribed clozapine for less than 8 weeks. Among 492 individuals prescribed clozapine for less than 8 weeks, there were no violent offences during the mirror image observation time before initiation, and 4 offences in the mirror image observation time following initiation.

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DISCUSSION

Summary of findings

In the population of Sweden, clozapine treatment was associated with greater reductions in overall and violent offending, but not non-violent offending, compared to olanzapine, the most commonly prescribed antipsychotic drug in Sweden. This was not accounted for by confounding by time-changing socioeconomic characteristics. ~~There was statistical evidence in favour of greater effects for clozapine than olanzapine on violent offending in those with a substance disorder, and for those with alcohol use- and cannabis use- disorders specifically. In contrast,~~E~~-e~~ffects of clozapine on non-violent offending were statistically similar to olanzapine, suggesting that clozapine may offer specific benefits on the risk of violent offending in people with psychotic disorders.

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Limitations and Strengths

There may be local factors that determine clozapine prescription, and our sample may not be representative of clozapine users outside Sweden. Our results, in particular the estimates of pre-treatment rate of offences, could have been affected by an underlying trend towards less offending in patients with psychotic disorders as they get older, irrespective of how they are treated. ~~.~~ Initiation of treatment in some individuals could have occurred as a result of violent behaviour, for example triggering arrest and subsequent psychiatric evaluation. We did not assess the effect of concurrent medicines in this study, including the effect of concurrent treatment with clozapine and olanzapine~~.~~. Although data on psychiatric diagnoses was comprehensive, misclassification is a possibility. A validation study involving record review of admission diagnoses in Sweden suggested good correspondence, with kappa values of between 0.74 and 0.76[31]. Around 85% of patients with an admission diagnosis of schizophrenia in Sweden had DSM-IV schizophrenia diagnoses assigned by clinical raters, in another study[32]. ~~However, although register-derived psychiatric diagnoses display reasonable correspondence with clinical diagnoses, admission diagnoses of substance use disorders,~~

~~may only capture more severe cases of substance misuse; effects identified for clozapine on offending in those with this outcome may therefore not be generalizable to those with substance use disorders who have not experienced admission for a substance use disorder.~~ Although adjustment was made for time-varying covariates, factors such as age, gender, and calendar time could not be examined directly, due to the chosen design. Mirror-image studies cannot take account of the possible effects of health policy changes on the background rates of the outcome. Adjusted estimates should therefore be interpreted with caution[33]. However, we were primarily interested in comparison between clozapine and olanzapine. We think the influence of these factors are likely to have been similar between the two treatment groups, and therefore unlikely to fully explain differences between olanzapine and clozapine treatment observed in this study. We included prescribing data from 2006; having such data prior to 2006 would have afforded a longer study period, and increased the ability to assess the impact on our results of change in underlying offending patterns over time. It is possible that predictors of offending that were not accounted for in this study, such as personality disorders or cognitive impairment, could have affected our results. We included only patients treated for longer than 8 weeks in our analysis – limiting the generalizability of our findings to people receiving treatment for at least this length of time. No violent offences occurred in mirror image observation times among individuals prescribed clozapine for less than 8 weeks. Prior to the availability of inpatient prescription data in 2006, patients may have initiated clozapine/olanzapine during an inpatient admission, but received the first recorded prescription only after discharge, resulting in a start time for the mirror image observation period which was later than the true start time for the drug, and misclassification of time on treatment as time off treatment. Any bias introduced by this would likely be towards underestimating the effectiveness of both drugs."

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On the other hand, our analysis was based on dates for offences rather than convictions in contrast with previous population-based studies, although we did not distinguish among offences comprising a conviction, beyond the classification of offences into violent and non-violent. Offences data ~~was~~ were taken from a whole population based register of convictions

with effectively total coverage; bias introduced by missing data on convictions is very unlikely. We had information on women, in contrast to one previous study on this topic in Sweden[15] that was restricted to men, and had access to enough data on clozapine to arrive at a precise estimate of rate reduction of violent offences attributable to clozapine treatment. Information on convictions and their aligned offences was from a national register of court proceedings, not based on self-report. We studied both overall and violent offences as the outcome. Our data were based on dispensed prescriptions for these drugs, and made the assumption that dispensing of the drug was equivalent to full adherence, making it analogous to an intention to treat analysis.

Explanations

~~The mechanisms by which psychosis leads to violent behaviours are largely unclear.~~ ~~However~~The observed~~,~~ reduction in violent offending rate for both antipsychotic drugs indicates that this could be a class effect of antipsychotic drugs as a whole, with clozapine being particularly effective, consistent with the superiority of clozapine over other antipsychotics in other areas[34, 35]. Clozapine could improve engagement with healthcare staff, social cognition, reduce irritability, improve social and occupational functioning, or effects on psychotic symptoms could mediate the effect. Clozapine-treated patients are typically affected by more severe illness and more treatment resistant symptoms, and clozapine treatment requires greater contact with the mental health system. In this regard, the current study was not able to distinguish among possible active components of clozapine treatment in relation to offending, including the role of increased contact with the health care system. One future approach to examining this could be to compare clozapine with another treatment that also involves increased contact with the health care system, such as long-acting injections (LAI). ~~We observed larger rate reductions for clozapine among those with comorbid substance use disorders compared to psychotic disorders as a whole, implying that the benefits of clozapine on broader social functioning might be related to changes in lifestyle/substance dependence comorbidity.~~

Previous literature

There is a consistent observational association between psychotic disorders and violence[3]. Violence risk in psychotic disorders may be related to clinical status[36], concurrent substance use disorders, or to non-adherence with antipsychotic medication[5]. Although Swanson et al [6] found that the violence reducing effects of atypical antipsychotics was greater than for typicals, an analysis of CATIE trial data by the same investigators indicated that violence reduction in newer antipsychotics was not significantly greater than for perphenazine, a traditional typical antipsychotic drug[37]. Convictions may happen a significant period of time after the offences themselves, leading to bias in effect estimates; the present study analysed date information on offences within convictions, and therefore benefited from greater statistical power. In contrast to previous work, the present study also adjusted for employment, salary presence, unemployment benefits, and place of residence as time-changing covariates that may have had an influence both on prescription of each drug and the offending outcome. Typically, measurement of violence in pharmacological studies has been done by independent observers using rating scales; few studies have used legal/administrative outcomes such as criminal conviction[5]. Stevens et al report a randomised controlled trial showing no effect of assertive specialized treatment on offending in first episode psychosis patients, suggesting the need for specific, rather than universal interventions for violence reduction[38].

How our results fit in

As far as we are aware, this is the first report of violence reducing effects of clozapine in a population-based sample of both men and women and in a within-subject observational design. We also found an (albeit weaker) effect for olanzapine, in accordance with some previous work[6]. Our results suggest that the effects are independent of socioeconomic factors that might also have an influence on offending rates.

CONCLUSIONS

We found strong statistical evidence for a violence reducing effect of clozapine in whole population data from Sweden that was larger in magnitude than olanzapine. Clozapine may be more effective than olanzapine at reducing violent offending behaviour.

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Table 1. Coding of offences used in this study

Violent offences	Manslaughter
	Homicide
	Gross assault
	Arson
	Infanticide
	Assault
	Cruelty to animals
	Sexual crimes
	Murder by carelessness
	Unlawful threat
	Weapon-related crime
	Assault on a public official
	Robbery
Non-violent offences	Acquisitive offence
	Vehicle offence
	Theft
	Disorderly conduct
	Contact ban
	False alarm
	Drug offence

Table 2. Description of clozapine(n=1004) and olanzapine (n=2256) and samples by non-time changing characteristics, based on prescription registers for the whole of Sweden, reflecting first withdrawal of each drug between 1st January 2006 to 31st December 2010

	Clozapine	Olanzapine
	Count(%)	Count (%)
Year of treatment start		
2006	204(20.32)	664(29.41)
2007	194(19.32)	490(21.7)
2008	201(20.02)	360(15.94)
2009	213(21.22)	372(16.47)
2010	192(19.12)	372(16.47)
Gender		
Male	663(66.04)	1385(61.34)
Female	341(33.96)	873(38.66)
Born in Sweden	797(79.38)	1721(76.22)
Duration of treatment		
8 weeks-1 year	224(22.31)	1001(44.33)
1 year – 3 years	446(44.42)	788(34.90)
3 years or more	334(33.27)	469(20.77)

Educational attainment at treatment start		
≤ 9 years	343(34.16)	702(31.09)
10-12 years	576(57.37)	1317(58.33)
University or higher	53(5.28)	172(7.62)
Missing	32(3.19)	67(2.97)
Age at drug start(years)		
18<28	206(20.52)	295(13.06)
28<38	331(32.97)	578(25.6)
38<48	319(31.77)	920(40.74)
48<58	148(14.74)	465(20.59)
Start periods		
Before 2007	398(39.64)	1154(51.11)
After 2008	606(60.36)	1104(48.89)
Period of psychotic disorders diagnosis		
1970-1982	34(3.39)	102(4.52)
1983-1991	137(13.65)	295(13.06)
1992-2001	291(28.98)	585(25.91)
2002-	542(53.98)	1276(56.51)
Age at psychotic disorders diagnosis		
18<28	536 (53.39)	861(38.13)
28<38	310 (30.88)	763(33.79)
38<48	141 (14.04)	527(23.34)
48<58	17 (1.69)	107(4.74)

Table 3. Descriptive data (absolute counts and rate of offences per 1000 person years of observation) for overall, violent, and non-violent offences for olanzapine (n=2258) and clozapine treatment (n=1004). Also shown are crude and adjusted offence (overall, non-violent, and violent) rate ratios with 95% confidence intervals for during vs before treatment with clozapine and olanzapine.

	Clozapine		Olanzapine		Interaction term	P value for interaction
Total number of violent offences	103		506			
Individuals with any violent offence(percentage of the overall treatment group)	63(6.27)		144(6.38)			
Number of violent offences before treatment (rate)	96(74.41)		376(95.71)			
Number of violent offences during treatment (rate)	7(5.43)		130(33.09)			
Effect of drug on violent offence rate	RR	95% CI	RR	95% CI		
Crude	0.07	0.03 , 0.18	0.35	0.20 , 0.61		
Fully adjusted[a]	0.13	0.05 , 0.34	0.82	0.47 , 1.43	4.82(1.56,14.86)	p=0.002
Total number of non-violent offences	222		507			
Individuals with any non-violent offence(percentage of the overall treatment group)	69(6.87)		193(8.55)			
Number of non-violent offences before treatment (rate)	161(124.79)		326(82.99)			
Number of non-violent offences during treatment (rate)	61(47.28)		181(46.07)			
Effect of drug on non-violent offence rate	RR	95% CI	RR	95% CI		
Crude	0.38	0.17 ,0.83	0.56	0.40 0.76		
Fully adjusted[a]	0.37	0.17 ,0.80	0.61	0.44 ,0.86	1.66(0.68,4.04)	p=0.263
Total number of overall offences	369		960			
Individuals with any overall offence(percentage of the overall treatment group)	128(12.75)		304(13.46)			
Number of overall offences before treatment (rate)	295(122.69)		635(161.64)			
Number of overall offences during treatment (rate)	74(30.78)		325(82.73)			
Effect of drug on overall offence rate	RR	95% CI	RR	95% CI		
Crude	0.25	0.12 ,0.51	0.51	0.12 ,0.51		
Fully adjusted[a]	0.24	0.12 ,0.48	0.62	0.45 , 0.85	2.55(1.20,5.44)	p=0.015

Rate ratios were estimated from zero-inflated negative binomial regression models with offence rate as the dependent variable and period of observation (dichotomised into before treatment and during treatment), as the main independent variable of interest.

Models took account of clustered before and during treatment data within individuals. Model estimates for zeroes are presented in table 1 of the Supplementary material.

a. Fully adjusted models are adjusted for urban residence, salary presence, employment status, and unemployment benefit receipt.

SUPPLEMENTARY MATERIAL

Table S1. Description of time-changing variables for each drug. "Before" variables reflect 2 years before start date of the drug, and "during" values reflect characteristics at the time of drug start.

	Clozapine		Olanzapine	
	Before (%)	During (%)	Before (%)	During (%)
Employment status				
Working	88(8.76)	69(6.87)	336(14.88)	287(12.71)
Not working but paying tax	76(7.57)	36(3.59)	207(9.17)	139(6.16)
Not working, not paying tax	829(82.57)	897(89.34)	1677(74.27)	1821(80.65)
Missing	11(1.10)	2(0.20)	38(1.68)	11(0.49)
Salary presence				
No	834(83.07)	905(90.14)	1708(75.64)	1846(81.75)
Yes	159(15.84)	97(9.66)	512(22.67)	401(17.76)
Missing	11(1.10)	2(0.20)	38(1.68)	11(0.49)
Social income (quintiles)				
1	185(18.43)	158(15.74)	331(14.66)	279(12.36)
2	193(19.22)	205(20.42)	321(14.22)	358(15.85)
3	218(21.71)	248(24.70)	526(23.29)	556(24.62)
4	200(19.92)	183(18.23)	588(26.04)	588(26.04)
5	197(19.62)	208(20.72)	454(20.11)	466(20.64)
Missing	11(1.10)	2(0.20)	38(1.68)	11(0.49)
Urban residence				
No	744(74.10)	760(75.70)	1673(74.09)	1687(74.71)
Yes	249(24.80)	242(24.10)	547(24.22)	560(24.80)
Missing	11(1.10)	2(0.20)	38(1.68)	11(0.49)
Total	1004(100)	1004(100)	2258(100)	2258(100)

McNemar test comparisons for before compared to during treatment, for employment and for the presence of salary were <0.001 for both clozapine, and olanzapine. For social income, p values for McNemar test were 0.246 for clozapine and <0.001 for olanzapine. P values for comparison of urban residence was 0.632 for clozapine, and 0.827 for olanzapine

Table S2. Final fully adjusted model estimates predicting zero offences, from zero-inflated negative binomial regression for violent, non-violent and overall offences

	Violent offences				Non-violent offences				Overall			
	Logit coefficient	P	Lower 95%CI	Upper 95%CI	Logit coefficient	P	Lower 95%CI	Upper 95%CI	Logit coefficient	P	Lower 95%CI	Upper 95%CI
Female gender	2.31	0.027	0.26	4.36	12.71	0.062	-0.61	26.03	15.21	0.207	-8.42	38.85
Age in years	0.06	0.083	-0.01	0.12	0.04	0.511	-0.07	0.15	0.04	0.099	-0.01	0.10
Dispersion parameter	17.37		8.59	35.14	27.11		20.92	35.13	19.47		16.07	23.60

Table S3. Descriptive data (absolute counts and rates per 1000 person years) for overall, violent, and non-violent offences for men with olanzapine (n=1385) and clozapine treatment (n=413). Also shown are crude and adjusted offence (overall, non-violent, and violent) rate ratios with 95% confidence intervals for during vs before treatment with clozapine and olanzapine.

	Clozapine		Olanzapine		Interaction term	P value for interaction
Total number of violent offences	88		411			
Individuals with any violent offence(percentage of the overall treatment group)	53(12.83)		123(8.88)			
Number of violent offences before treatment (rate)	85(81.76)		308(161.63)			
Number of violent offences during treatment (rate)	3(2.89)		103(54.05)			
Effect of drug on violent offence rate	RR	95% CI	RR	95% CI		
Crude	0.04	0.01 ,0.12	0.34	0.20 ,0.57		
Fully adjusted[a]	0.03	0.01 ,0.11	0.38	0.21 ,0.69	11.03(3.01,40.35)	<0.001
Total number of non-violent offences	172		375			
Individuals with any non-violent offence(percentage of the overall treatment group)	50(12.11)		152(10.97)			
Number of non-violent offences before treatment (rate)	126(121.20)		240(96.35)			
Number of non-violent offences during treatment (rate)	46(44.25)		135(54.20)			
Effect of drug on non-violent offence rate						
Crude	0.37	0.15 ,0.91	0.56	0.40 ,0.80		
Fully adjusted[a]	0.36	0.14 ,0.89	0.64	0.43 ,0.95	1.78(0.61,5.22)	0.288
Total number of overall offences	298		744			
Individuals with any overall offence(percentage of the overall treatment group)	101(24.46)		250(18.05)			
Number of overall offences before treatment (rate)	243(149.94)		498(199.93)			
Number of overall offences during treatment (rate)	55(33.94)		246(98.76)			
Effect of drug on overall offence rate	RR	95% CI	RR	95% CI		
Crude	0.23	0.10 ,0.52	0.49	0.36 ,0.68		
Fully adjusted[a]	0.22	0.10 ,0.50	0.54	0.37 ,0.78	2.45(0.95,6.32)	0.064

Rate ratios were estimated from zero-inflated negative binomial regression models with offence rate as the dependent variable and period of observation within mirror image observation time (dichotomised into before treatment and during treatment), as the main independent variable of interest. Models took account of clustered before and during treatment data within individuals.

a. Fully adjusted models are adjusted for urban residence, salary presence, employment status, and unemployment benefit receipt.

Table S4. Descriptive data (absolute counts and rates per 1000 person years) for overall, violent, and non-violent offences for women with olanzapine (n=873) and clozapine treatment (n=105). Also shown are crude and adjusted offence (overall, non-violent, and violent) rate ratios with 95% confidence intervals for during vs before treatment with clozapine and olanzapine.

	Clozapine	Olanzapine	Interaction term	P value for interaction
Total number of violent offences	15	95		
Individuals with any violent offence(percentage of the overall treatment group)	10(9.52)	21(2.41)		
Number of violent offences before treatment (rate)	11(43.89)	68(56.39)		

Number of violent offences during treatment (rate)	4(15.96)		27(22.39)			
Effect of drug on violent offence rate	RR	95% CI	RR	95% CI		
Crude	0.38	0.10 ,1.46	0.41	0.07 ,2.38		
Fully adjusted[a]	0.34	0.08 ,1.39	0.55	0.09 ,3.30	1.63 (0.16, 16.61)	0.681
Total number of non-violent offences	50		132			
Individuals with any non-violent offence(percentage of the overall treatment group)	19(18.10)		41(4.70)			
Number of non-violent offences before treatment (rate)	35(139.66)		86(59.83)			
Number of non-violent offences during treatment (rate)	15(59.85)		46(32.00)			
Effect of drug on non-violent offence rate						
Crude	0.44	0.09 ,2.04	0.54	0.26 ,1.08		
Fully adjusted[a]	0.40	0.08 ,2.04	0.60	0.32 ,1.11	1.51(0.26,8.78)	0.648
Total number of overall offences	71		216			
Individuals with any overall offence(percentage of the overall treatment group)	27(25.71)		54(6.19)			
Number of overall offences before treatment (rate)	52(66.35)		137(95.30)			
Number of overall offences during treatment (rate)	19(24.24)		79(54.96)			
Effect of drug on overall offence rate						
Crude	0.37	0.10 ,1.39	0.58	0.27 ,1.27		
Fully adjusted[a]	0.35	0.09 ,1.38	0.55	0.30 ,1.01	1.56(0.35,6.96)	0.558

Rate ratios were estimated from zero-inflated negative binomial regression models with offence rate as the dependent variable and period of observation within mirror image observation time (dichotomised into before treatment and during treatment), as the main independent variable of interest. Models took account of clustered before and during treatment data within individuals.
a. Fully adjusted models are adjusted for urban residence, salary presence, employment status, and unemployment benefit receipt.

Table S5. Descriptive data (absolute counts and rates per 1000 person years) for overall, violent, and non-violent offences for women with olanzapine (n=1789) and clozapine treatment (n=333) among those with mirror image observation times of less than three years. Also shown are crude and adjusted offence (overall, non-violent, and violent) rate ratios with 95% confidence intervals for during vs before treatment with clozapine and olanzapine.

	Clozapine		Olanzapine		Interaction term	P value for interaction
Total number of violent offences	28		269			
Individuals with any violent offence(percentage of the overall treatment group)	21(6.31)		90(5.03)			
Number of violent offences before treatment (rate)	24(49.15)		164(11.43)			
Number of violent offences during treatment (rate)	4(8.19)		105(70.70)			
Effect of drug on violent offence rate						
Crude	0.27	0.07 ,0.99	1.14	0.58 ,2.23		
Fully adjusted[a]	0.30	0.06 ,1.44	0.90	0.49 ,1.66	3.02(0.57,16.09)	0.194
Total number of non-violent offences	74		307			
Individuals with any non-violent offence(percentage of the overall treatment group)	31(9.31)		130(7.27)			
Number of non-violent offences before treatment (rate)	51(104.45)		183(98.63)			
Number of non-violent offences during treatment (rate)	23(47.10)		124(66.83)			
Effect of drug on non-violent offence rate						
Crude	1.20	0.28 ,5.22	0.91	0.59 ,1.39		

Fully adjusted[a]	1.01	0.19	5.49	1.03	0.72	,1.49	1.02(0.19,5.52)	0.980
Total number of overall offences	120			560				
Individuals with any overall offence(percentage of the overall treatment group)	51(15.32)			203(11.35)				
Number of overall offences before treatment (rate)	90(94.65)			330(178.13)				
Number of overall offences during treatment (rate)	30(31.55)			230(124.02)				
Effect of drug on overall offence rate								
Crude	0.62	0.06	,6.81	1.10	0.73	,1.65		
Fully adjusted[a]	0.51	0.06	,4.50	1.12	0.75	,1.68	2.20(0.24,19.80)	0.482

Rate ratios were estimated from zero-inflated negative binomial regression models with offence rate as the dependent variable and period of observation within mirror image observation time (dichotomised into before treatment and during treatment), as the main independent variable of interest. Models took account of clustered before and during treatment data within individuals.
a. Fully adjusted models are adjusted for urban residence, salary presence, employment status, and unemployment benefit receipt.

Table S6. Descriptive data (absolute counts and rates per 1000 person years) for overall, violent, and non-violent offences for women with olanzapine (n= 469) and clozapine treatment (n= 185) among those with mirror image observation times of three years or greater. Also shown are crude and adjusted offence (overall, non-violent, and violent) rate ratios with 95% confidence intervals for during vs before treatment with clozapine and olanzapine.

	Clozapine			Olanzapine			Interaction term	P value for interaction
Total number of violent offences	75			237				
Individuals with any violent offence(percentage of the overall treatment group)	42(22.70)			54(11.51)				
Number of violent offences before treatment (rate)	72(89.79)			212(130.35)				
Number of violent offences during treatment (rate)	3(3.74)			25(15.37)				
Effect of drug on violent offence rate								
Crude	0.04	0.01	,0.14	0.12	0.05	,0.26		
Fully adjusted[a]	0.04	0.01	,0.12	0.13	0.06	,0.28	3.64(0.93,14.27)	0.063
Total number of non-violent offences	148			200				
Individuals with any non-violent offence(percentage of the overall treatment group)	38(20.54)			63(13.43)				
Number of non-violent offences before treatment (rate)	110(137.17)			143(68.98)				
Number of non-violent offences during treatment (rate)	38(47.39)			57(27.50)				
Effect of drug on non-violent offence rate								
Crude	1.29	0.49	,3.36	0.69	0.33	,1.47		
Fully adjusted[a]	1.20	0.48	,3.04	0.78	0.40	,1.55	0.65(0.18,2.39)	0.517
Total number of overall offences	249			400				
Individuals with any overall offence(percentage of the overall treatment group)	77(41.62)			101(21.54)				
Number of overall offences before treatment (rate)	205(141.04)			305(147.12)				
Number of overall offences during treatment (rate)	44(30.27)			95(45.83)				
Effect of drug on overall offence rate								
Crude	0.91	0.18	,4.59	0.60	0.34	,1.04		
Fully adjusted[a]	0.82	0.16	,4.13	0.66	0.38	,1.14	0.81(0.13,4.88)	0.818

Rate ratios were estimated from zero-inflated negative binomial regression models with offence rate as the dependent variable and period of observation within mirror image observation time (dichotomised into before treatment and during treatment), as the main independent variable of interest. Models took account of clustered before and during treatment data within individuals.
a. Fully adjusted models are adjusted for urban residence, salary presence, employment status, and unemployment benefit

receipt.