Psychotropic Medications in Swedish Homicide Victims and Offenders:

A Forensic-Toxicological Case-Control Study of Adherence and Recreational Use

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ABSTRACT

Objective: We aimed to assess the extent to which adherence to, and recreational use of, psychotropic medications influence the risk of homicide offending and victimization.

Methods: We conducted a population-based case-control study by way of linking a nationwide registry of dispensed prescriptions with a forensic-toxicological database. Homicide victims (n = 200) and offenders (n = 105) were identified for the years 2007–2009 and vehicle-accident controls (n = 1,643) for the years 2006–2013. The occurrence of congruence and incongruence between dispensed prescriptions and toxicology was used as a measure of adherence and recreational use.

Results: For antidepressants, incongruence—but not congruence—between dispensed prescriptions and toxicology was associated with a significantly increased risk of homicide offending (odds ratio adjusted for age and sex [aOR] = 6.2; 95% confidence interval [CI], 3.3–11.6) but not homicide victimization (aOR = 0.8; 95% CI, 0.3–2.0). For antipsychotics and mood stabilizers, a significantly increased risk of homicide offending was associated with incongruence between prescriptions and toxicology (aOR = 7.0; 95% CI, 2.8–17.7), whereas risk estimates for congruence were not significantly elevated for either homicide offending or victimization. For GABAergic hypnotics, congruence and incongruence were significantly associated with increased risks of both homicide offending (aOR = 5.4; 95% CI, 2.6–11.0 and aOR = 4.9; 95% CI, 2.6–9.3, respectively) and homicide victimization (aOR = 2.1; 95% CI, 1.1–4.2 and aOR = 3.2; 95% CI, 1.7–6.1, respectively). Sensitivity analyses with a subset of controls yielded similar estimates.

Conclusions: Nonadherence to medications used to treat affective and psychotic disorders appears to elevate the risk of homicide offending. Both medicinal and recreational use of GABAergic hypnotics appears to elevate the risk of homicide offending and victimization. In summary, vigilance regarding adherence to medications prescribed for mood disorders and psychosis, as well as restrictiveness regarding licit and illicit access to addictive hypnotics, might contribute to a reduction of homicidal violence.

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Compelling data suggest a link between mental illness and violence and homicide among both victims and offenders.[1–4] In a study from the United States, 58% of homicide offenders had at some time been diagnosed with a psychiatric disorder[5]; the rate in Sweden was found to be even higher, at 90%, in a sample that also included perpetrators of attempted homicide.[6] Moreover, a study from England and Wales has shown that almost 10% of homicide offenders were found to suffer from a psychotic disorder,[7] although it is a topic of ongoing debate whether such disorders confer a heightened violence risk in the absence of comorbid substance misuse.[2,8] In a recent meta-analysis, Coid and coworkers uncovered a robust, independent association between paranoid ideation and violence[8]; however, the association between psychotic disorders and violence remained dependent upon other factors, in accordance with previous findings.[9] Violent offending has been linked not only to psychotic states,[10] but also to depression[11] and to both the manic and the depressive phases of bipolar disorder.[12–14] Further, in a Danish cohort study, increased rates of violent offending were associated not only with mood disorders and psychosis, but also with a wide range of other psychiatric conditions.[15]

With regard to preventive efforts, a systematic review has identified nonadherence to medication as a risk factor for violence in psychotic patients.[10] In addition, a recent consensus paper concludes that prevention of homicidal behavior in males with psychiatric disorders should focus on facilitating compliance with long-term treatment in high-risk groups.[16] Indeed, a Swedish registry-based study that employed an intraindividual design found, in individuals treated with antipsychotics and mood stabilizers, reductions in violent criminality of 45% and 24%, respectively, during periods of treatment compared to periods off medication[17]—findings that imply an association between criminal offending and the disorders for which such medications are prescribed. However, it should be emphasized that the latter study[17] merely made use of prescription data—in the absence of biochemical confirmation of adherence by way of toxicological analysis—which raises a question as to what extent subjects had truly taken their medication. In our own previous toxicology-based study,[18] we found that benzodiazepine use occurred frequently among homicide victims and offenders; however, the study[18] did not include a control group, and without access to prescription data, we were unable to determine the extent to which medication use had been recreational.

Clinical Points

- The present study is the first to assess adherence to pharmacotherapy by comparing dispensed prescriptions with results from forensic-toxicological analyses.
- Nonadherence to treatment with antidepressants conferred a 6-fold risk, and nonadherence to treatment with antipsychotics or mood stabilizers a 7-fold risk, of homicide offending.
- Vigilance regarding adherence to medications prescribed for affective and psychotic disorders might contribute to a reduction of homicidal violence.

In this population-based study, using a case-control design, we linked data from a prescription registry and a toxicology database with a view to assessing the extent to which adherence to, and recreational use of, psychotropic medications influence the risk of homicide offending and victimization. On the basis of prior research,[1,2,4,6,18,21] we hypothesized that homicide offenders and victims, compared to vehicle-accident controls, would be less adherent with regard to medications used to treat affective and psychotic disorders yet more prone to engage in recreational use of addictive medications used to treat anxiety and sleep disorders.

METHODS

Setting

In Sweden, all suspected unnatural deaths are investigated by means of forensic-pathological autopsies conducted under the auspices of a governmental agency, the National Board of Forensic Medicine (NBFM). Autopsies are routinely augmented by forensic-toxicological analyses—performed at the NBFM's Department of Forensic Toxicology and Forensic Genetics and capable of detecting a wide range of licit and illicit substances—provided that an adequate biological specimen can be obtained; the same analyses are also performed on living subjects, including suspected offenders, upon request by the police. Analytic work was carried out at a central laboratory using methods that have remained largely unchanged during the study period. Since July 1, 2005, the Swedish Board of Health and Welfare has maintained a prescription registry that contains individual-level information on all dispensed prescriptions in the country, including those sold at privately operated pharmacies. In the present study, homicide is defined as murder, infanticide, voluntary manslaughter or involuntary manslaughter by means of assault; and offender is defined as a person either who has been found guilty of homicide or who, upon police investigation, was adjudged to have committed homicide followed by suicide. The study was approved by the Regional Ethical Review Board in Stockholm (reference numbers 2010/1764–31/5 and 2013/5:8).

Subjects

For all homicides committed in Sweden during the period January 1, 2007, to December 31, 2009, victims (n = 200) and offenders (n = 105) were included provided that they, at the time of the offense, were at least 18 years of age and had been assigned a Swedish personal identity number. Victims were identified in the NBFM in-house autopsy database and were required to have undergone autopsy augmented by forensic-toxicological analyses. Offenders were identified in the National Crime Registry, which is maintained by the Swedish National Council for Crime Prevention (www.bra.se), and were required to have undergone sampling within 48 hours post offense—lest toxicology fail to capture medication use at the time of the offense. Analogously, controls (n = 1,643), who were identified in the Cause of Death Registry (maintained by the National Board of Health and Welfare), were included provided that they had died at the scene of a vehicle-related accident, rather than in an ambulance or at a hospital post accident. Further, controls were required to have been at least 18 years of age; to have lost their lives in a vehicle-related accident during the period January 1, 2006, to December 31, 2013 (*ICD-9* codes E800–E848 and *ICD-10* codes V01–V99[19,20]); and to have undergone autopsy augmented by forensic-toxicological analyses, without having been assigned a code pertaining to definite or possible self-inflicted death by the forensic pathologist (*ICD-9* codes E950–E959 and E980–E989; and *ICD-10* codes X60–X84 and Y10–Y34[19,20]). For sensitivity analyses, a subset of controls—passengers and pedestrians involved in traffic accidents—was identified in the NBFM autopsy database.

For all study subjects, information regarding all prescriptions dispensed during the last 6 months (183 days) preceding the index event (ie, homicide or vehicle-related accident) was retrieved for the following categories of medication: antidepressants, antipsychotics and mood stabilizers (analyzed jointly, by virtue of their continuous use in chronic psychotic and affective disorders), and GABAergic hypnotics (benzodiazepines, as well as zopiclone and zolpidem).

Congruence between dispensed prescriptions and toxicological findings was used to assess adherence and recreational use; Table 1 presents numbers of homicide offenders, homicide victims, and vehicle-accident controls with dispensed prescriptions, by medication, and numbers of these subjects positive for the same medication or its metabolites upon forensic-toxicological examination. Some subjects were both congruent and incongruent with respect to different medications within the same pharmaceutical category; such individuals were, in analyses of adherence, adjudged to be congruent, but, in analyses of recreational use, adjudged to be incongruent.

Statistics

Odds ratios adjusted for age and sex (aORs) were calculated by means of logistic regression using SPSS version 22 for Mac and R version 3.1.0; aORs for which 95% confidence intervals (CIs) did not span unity were considered statistically significant. To assess risks of involvement in homicide associated with nonadherent and adherent use of antidepressants and mood stabilizers and antipsychotics,

Table 1. Numbers of Homicide Offenders, Homicide Victims, and Vehicle-Accident Controls With Dispensed Prescriptions, by Medication, and Numbers of These Subjects Positive for Same Medication or Its Metabolites on Forensic-Toxicological Examination

Medication	Offenders (n = 105)	Victims (n = 200)	Controls (n = 1,643)
Dispensed Prescriptions/Positive Toxicology			
Antidepressants			
Amitriptyline	1/0	1/0	10/5
Citalopram/escitalopram	6/2	6/6	57/40
Clomipramine	0/0	1/1	5/4
Fluoxetine	0/0	2/2	4/3
Mianserin	0/0	1/1	3/2
Mirtazapine	6/1	7/4	33/13
Moclobemide	0/0	1/1	1/0
Nortriptyline	1/0	0/0	0/0
Paroxetine	0/0	2/0	9/3
Reboxetine	0/0	1/0	3/1
Sertraline	7/1	2/1	27/16
Venlafaxine	4/2	1/1	23/18
Antipsychotics and mood stabilizers			
Carbamazepine	2/1	4/4	12/12
Chlorprothixene	0/0	0/0	3/3
Clozapine	0/0	0/0	1/1
Haloperidol	0/0	0/0	2/0
Lamotrigine	3/0	0/0	6/5
Levomepromazine	1/0	0/0	7/1
Melperone	0/0	0/0	1/0
Olanzapine	3/1	2/2	7/3
Quetiapine	3/1	0/0	8/3
Topiramate	0/0	0/0	2/2
Positive Toxicology/Dispensed Prescriptions			
GABAergic hypnotics			
Alprazolam	4/2	3/0	15/3
Clonazepam	1/0	3/0	15/4
Diazepam	18/8	7/3	40/21
Flunitrazepam	0/0	2/1	2/1
Nitrazepam	1/0	4/2	5/3
Oxazepam	2/1	0/0	8/5
Zolpidem	1/1	0/0	9/7
Zopiclone	3/1	8/7	26/22

logistic regression models were created that included, as predictors, congruence and incongruence between dispensed prescriptions and positive toxicology, and as outcome, homicide offending or victimization; because predictors took the form of dummy variables, the reference group consisted of subjects without dispensed prescriptions during the 6 months prior to the index event. In the same manner, to assess risks of involvement in homicide associated with recreational and medicinal use of GABAergic hypnotics, logistic regression models were created that included, as predictors, congruence and incongruence between positive toxicology and dispensed prescriptions, and as outcome, homicide offending or victimization; in this case, because predictors took the form of dummy variables, the reference group consisted of subjects with negative toxicology in connection with the index event.

RESULTS

Demographics

From a total of 1,948 study subjects (78.9% male; mean age = 47.7 years, standard deviation [SD] = 19.3 years), there were 105 offenders (91.4% male; mean age = 38.4 years, SD = 14.5 years), 200 victims (64.0% male; mean age = 44.6 years, SD = 17.3 years), and 1,643 controls (79.9% male; mean age = 48.7 years, SD = 19.6 years). A subset of controls used for sensitivity analyses comprised 294 individuals involved in accidents either as pedestrians or as passengers in vehicles (60.2% male; mean age = 50.3 years, SD = 21.5 years).

Table 2. Risks of Homicide Offending and Victimization Conferred by Adherence to, and Recreational Use of, Psychotropic Medications (as defined by congruence and incongruence between dispensed prescriptions and forensic-toxicological findings, respectively) in Homicide Offenders (n = 105) and Victims (n = 200) Compared to Vehicle-Accident Controls (n = 1,643)

Variable	Homicide Offending, aOR[a] (95% CI)	Homicide Victimization, aOR[a] (95% CI)
Adherence		
Antidepressants		
Congruence	1.2 (0.5–3.1)	1.2 (0.7–2.2)
Incongruence	6.2 (3.3–11.6)	0.8 (0.3–2.0)
Antipsychotics and mood stabilizers		
Congruence	3.0 (0.9–10.5)	2.3 (0.9–5.8)
Incongruence	7.0 (2.8–17.7)	…[b]
Recreational use		
GABAergic hypnotics		
Congruence	5.4 (2.6–11.0)	2.1 (1.1–4.2)
Incongruence	4.9 (2.6–9.3)	3.2 (1.7–6.1)

[a]Adjusted for age and sex.
[b]None of the victims was incongruent with respect to antipsychotics and mood stabilizers.
Abbreviations: aOR = adjusted odds ratio, CI = confidence interval.

Adherence

As seen in Table 2, congruence between dispensed prescriptions and positive toxicology for antidepressants did not significantly affect the risk of homicide offending (aOR = 1.2; 95% CI, 0.5–3.1) or homicide victimization (aOR = 1.2; 95% CI, 0.7–2.2); by contrast, incongruence (here, at least 1 dispensed prescription in the absence of positive toxicology) was associated with a significantly increased risk of homicide offending (aOR = 6.2; 95% CI, 3.3–11.6) but not homicide victimization (aOR = 0.8; 95% CI, 0.3–2.0). Similarly, incongruence between dispensed prescriptions and positive toxicology for antipsychotics and mood stabilizers was associated with a significantly increased risk of homicide offending (aOR = 7.0; 95% CI, 2.8–17.7), whereas congruence did not significantly affect the risk of either homicide offending (aOR = 3.0; 95% CI, 0.9–10.5) or homicide victimization (aOR = 2.3; 95% CI, 0.9–5.8). In summary, nonadherence to medications used to treat affective and psychotic disorders elevated the risk of homicide offending.

Recreational Use

As also seen in Table 2, both congruence and incongruence (here, positive toxicology in the absence of at least 1 dispensed prescription) between positive toxicology and dispensed prescriptions for GABAergic hypnotics were significantly associated with increased risks of both homicide offending

Table 3. Sensitivity Analyses: Risks of Homicide Offending and Victimization Conferred by Adherence to, and Recreational Use of, Psychotropic Medications (as defined by congruence and incongruence between dispensed prescriptions and forensic-toxicological findings, respectively) in Homicide Offenders (n = 105) and Victims (n = 200) Compared to Passenger and Pedestrian Controls (n = 294)

Variable	Homicide Offending, aOR[a] (95% CI)	Homicide Victimization, aOR[a] (95% CI)
Adherence		
Antidepressants		
Congruence	2.1 (0.6–7.2)	2.0 (0.9–4.6)
Incongruence	7.4 (2.8–19.8)	0.8 (0.3–2.3)
Antipsychotics and mood stabilizers		
Congruence	2.5 (0.5–12.6)	2.0 (0.6–6.8)
Incongruence	12.5 (2.3–68.0)	…[b]
Recreational use		
GABAergic hypnotics		
Congruence	8.7 (2.5–30.0)	4.6 (1.5–13.7)
Incongruence	4.5 (1.7–11.6)	3.0 (1.2–7.6)

[a]Adjusted for age and sex.
[b]None of the victims was incongruent with respect to antipsychotics and mood stabilizers.
Abbreviations: aOR = adjusted odds ratio, CI = confidence interval.

(aOR = 5.4; 95% CI, 2.6–11.0 and aOR = 4.9; 95% CI, 2.6–9.3, respectively) and homicide victimization (aOR = 2.1; 95% CI, 1.1–4.2 and aOR = 3.2; 95% CI, 1.7–6.1). In summary, both medicinal and recreational use of GABAergic hypnotics elevated the risk of homicide offending and homicide victimization.

Sensitivity Analyses

In order to investigate the robustness of the findings, sensitivity analyses were performed using a subset of controls in whom medication-taking behavior was assumed to have had less impact on the outcome than in the entire population of controls—individuals who were involved in accidents either as pedestrians or as passengers in vehicles (Table 3). Estimated risks were of the same order of magnitude as in the primary analyses, with 2 notable exceptions—when homicide offenders were compared to passenger and pedestrian controls, the risk estimate for incongruence between dispensed prescriptions and positive toxicology was nearly doubled with respect to antipsychotics and mood stabilizers (aOR = 12.5; 95% CI, 2.3–68.0); similarly, when the same groups were compared with regard to GABAergic hypnotics, the risk estimate for congruence between dispensed prescriptions and toxicology was nearly doubled (aOR = 8.7; 95% CI, 2.5–30.0). As expected, for all estimates, CIs were wider than in the primary analyses.

DISCUSSION

To our knowledge, this is the first population-based study—of any biological or behavioral phenotype—to exploit discrepancies between prescription and toxicology data in order to uncover suboptimal adherence to pharmacotherapy. By comparing adherence rates in subjects involved in homicide and vehicle-accident controls, we found that nonadherence to treatment with antidepressants conferred a statistically significant 6-fold risk, and nonadherence to treatment with antipsychotics or mood stabilizers a statistically significant 7-fold risk, of homicide offending. Meanwhile, with regard to adherent use of the same medications, risk estimates ranged between 1 and 3 in victims and offenders, with 95% CIs overlapping unity. Finally, both medicinal and recreational use of GABAergic hypnotics conferred statistically significant 2-fold to 5-fold risks of both homicide offending and victimization. Analyses were adjusted for age and sex but not for other potentially important confounders. Although previous research has described similar associations between suboptimal compliance and involvement in homicide,[21] our ambition has been to characterize the phenotypes of homicide offenders and victims through the use of a control group presumed to reflect conditions in the general population, allowing both specification of risk estimates and speculations about causality.

Implications

It is reasonable to assume that both substance misuse[22] and socioeconomic factors—including inequalities with regard to education, income, and access to social services—unadjusted for in the present study, may influence both medicinal compliance and involvement in criminal violence; moreover, recent research has highlighted the influence of additional, familial confounding on risk estimates regarding deviant behavior.[23] Nevertheless, the results of the present study also appear to be intuitively sound. In all likelihood, a substantial proportion of the study subjects prescribed antidepressants, antipsychotics, or mood stabilizers had been diagnosed with depression, psychosis, or bipolar disorder; as mentioned previously, these conditions are associated with an increased risk of violence,[9–15] and discontinued treatment can be assumed to elevate the risk even further. By contrast, as indicated by similar risk estimates for medicinal and recreational use, ongoing consumption, either licit or illicit, of GABAergic hypnotics increased the risk of involvement in homicide; however, this finding, too, is hardly surprising given the known pharmacodynamic properties of benzodiazepines and Z drugs, which include disinhibition of violent impulses.[24]

Limitations

Although the present study benefits from low selection bias on account of its population-based design, there are other aspects of its methodology that may have diminished the accuracy of risk estimates. For example, the study does not include information on medication received during inpatient care; given known associations between mental illness and violence, it is conceivable that cases may have received such care more frequently than controls—a discrepancy whose net effect on estimates, however, is difficult to predict. Further, by focusing on prescriptions dispensed during the 6 months prior to the index event, we may have misclassified subjects with older, yet still valid,

prescriptions. Conversely, misclassification may also have occurred in subjects with recently dispensed prescriptions whose treatment nonetheless had been discontinued upon renewed contacts with health care services. However, there is no reason to suspect that either type of misclassification would have affected cases and controls unequally.

Toxicological analyses can only indicate medication use during a short period of time preceding specimen sampling; however, in reality, adherence is a broader phenomenon, defined by the World Health Organization as "the extent to which a person's behavior [including taking medication] corresponds with agreed recommendations from a healthcare provider."[25(p3)] Although there is no generally accepted gold standard for assessing adherence, the use of a combination of direct and indirect measures—for example, toxicology and prescription data, as in the present study—has been advocated to increase the validity of estimates.[26] Further, owing to the nature of our dataset, we were unable to investigate the influence of primary nonadherence—ie, the failure to get a prescription filled—on the risk of involvement in homicide; however, by focusing on secondary nonadherence—ie, the failure to take medications after filling a prescription—we may have uncovered risks more specifically associated with initiated, yet subsequently discontinued, treatment.

Ideally, a control group should be randomly selected from the source population that gives rise to cases.[27] Unfortunately, owing to our need to obtain forensic-toxicological data, that condition could not be met. However, since vehicle-related accidents occur suddenly and unexpectedly, the risk of altered medication-taking behavior prior to sampling ("white coat adherence") has most likely been minimized. Moreover, such controls can arguably be regarded as a representative sample of ambulant, community-dwelling adults.

CONCLUSIONS

In the present study, we confirmed the hypotheses that, compared to vehicle-accident controls, homicide offenders would be less adherent with regard to medications used to treat affective and psychotic disorders, and both homicide offenders and victims would be more prone to engage in recreational use of addictive medications used to treat anxiety and sleep disorders. The hypothesis that homicide victims would be less adherent to medications used to treat affective and psychotic disorders was, however, not confirmed. Sensitivity analyses established the robustness of these results and, indeed, implied that we, in our primary analyses, may have underestimated the risks of homicide offending conferred by nonadherence to psychopharmacologic treatment.

Policy makers and health care providers should be alerted to the fact that vigilance regarding adherence to medications prescribed for affective and psychotic disorders, as well as restrictiveness regarding licit and illicit access to addictive hypnotics, might contribute to a reduction of homicidal violence.

Future Directions

Importantly, our results must be treated with caution prior to replication. Future studies should ideally be undertaken in the context of international collaborative efforts using uniform definitions of variables and larger samples that span longer recruitment periods. Moreover, by incorporating data from health care records and by adjusting for additional potential confounders, including substance misuse and socioeconomic variables, it would be possible to better assess the validity of prescriptions and to increase the precision of risk estimates, allowing sounder speculations about causality.

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