General Hospital Psychiatry 59 (2019) 81–82

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Letter to the Editor

Does a history of violence predict higher antipsychotic dosage in schizophrenia?

To the Editor,

Schizophrenia is a psychiatric disorder characterized by diverse and complex symptoms, including aggression and violence. Due to early disease onset and persistence of such symptoms, there remains a high median lifetime morbid risk of 7.2 per 1000 people [1]. Although violence is expressed in a minority of patients with schizophrenia, the frequency is disproportionately higher than in patients with other psychiatric disorders [2]. An important risk factor for these behaviors is poor adherence to antipsychotic medications [3].

For instance, oral clozapine, a second-generation antipsychotic, has been shown to have ameliorating effects in reducing persistent aggressive and violent behavior [4]. However, use of such antipsychotics has been associated with side effects, including weight gain, hyperlipidemia, and extrapyramidal symptoms [5]. These side effects contribute to poor adherence with oral antipsychotics and eventual treatment termination, thus increasing the risk for rehospitalization and relapse [6]. Long-acting injectable (LAI) antipsychotics were introduced to address the issue of non-adherence. While the frequency of injections varies by LAI formulation, patients, instead of taking oral medications once or even twice per day, can receive LAI administrations up to once every 4 weeks. Studies have suggested that the use of LAI antipsychotics is associated with lower rates of psychiatric relapse compared to their oral counterparts [7].

Currently, there are no published trials exploring the efficacy of LAI antipsychotics in reducing chronic aggressive and violent behavior. This gap in literature results in a lack of clear guidelines for the treatment of violence with LAI formulations. In a first step to address this gap, there is a need for understanding the impact of a history of violence on prescribed antipsychotic regimen. We hypothesize that the prescription of LAIs and higher antipsychotic dosage are dependent on a patient's history of violence.

A cohort of 286 participants between the ages of 18 and 75 was recruited from the Centre for Addiction and Mental Health (CAMH) in Toronto. All participants met the criteria for a clinical diagnosis of schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for DSM-IV (SCID-I/P). The study was approved by the CAMH Research Ethics Board and written informed consent for study participation and disclosure of personal health records was obtained.

Aggression was assessed retrospectively by scoring the severity of the worst episode of aggression lifetime documented in participants' medical records using an adapted form of the Modified Overt Aggression Scale (MOAS). The MOAS measures verbal, property, and physical aggression over the past week, though it was adapted to consider the entire lifetime. Individual scores were assigned for each of the verbal, property, and physical categories on a scale from 0 to 4, with 4 being the most severe. History of physical violence, or any violent action intended to inflict bodily harm upon another, was defined as a binary variable based on a zero or non-zero physical aggression score.

In addition, other clinically-relevant predictors were evaluated as covariates: demographics; family history with the Family Interview for Genetics Studies (FIGS); early life adversities with the Childhood Trauma Questionnaire (CTQ); and comorbid diagnoses of substance abuse with the SCID-I/P. The prescribed antipsychotics and dosages were recorded from medical records and converted to chlorpromazine equivalents (CPZe).

To determine whether the history of physical violence, verbal aggression, or other clinical factors have significant value in predicting LAI treatment and higher antipsychotic dosage, logistic and linear regression models were performed using IBM SPSS® Statistics v24.0.

In brief, the 286 participants (70% male, 30% female) were classified as having a history of physical violence (n = 120) and no history of physical violence (n = 166). Demographics and clinical data of study participants are summarized in Supplementary Table S1.

We found a trend for statistical significance in the association between history of physical violence (binary) and current LAI treatment (p = 0.088). Interestingly, the individual scores for verbal, property, and physical aggression were each significant for the prediction of current LAI treatment (Table 1). Furthermore, a diagnosis of non-cannabis drug abuse or dependence was significantly associated with LAI treatment.

Our results also showed a trend for statistical significance in the association between higher CPZe and presence of physical violence (p = 0.052). However, only the individual verbal and physical aggression scores were found to be significantly associated with higher dosages (Table 2). Notably, age was also significantly associated with higher CPZe dosage.

Overall, the presence of lifetime physical violence was a moderate predictor of LAI treatment and higher antipsychotic dosage. While the association was only slightly significant, it could be a result of underpowered tests due to small sample size. However, there was a strong association between higher individual aggression scores and both LAI treatment and increased dosage.

Use of illicit substance is a known risk factor for violence in patients with schizophrenia [8]. Our finding that non-cannabis drug abuse or dependence is strongly associated with LAI treatment appears to strengthen the relationships among substance abuse or dependence, violence, and LAI treatment. The finding that age was associated with higher CPZe dosages is not consistent with the literature that younger patients may receive higher antipsychotic dosages [9]. Finally, the finding that suicide attempters are associated with higher dosage could support a relationship between higher dosage and resulting increased side effects contributing to increased suicide risk.

As an observational study, a wide spectrum of antipsychotics was incorporated in the analysis, including clozapine with its anti-aggression effects [4]. However, there exist several limitations in this study. No criteria were established regarding the duration of time for which

https://doi.org/10.1016/j.genhosppsych.2019.01.004
Received 22 August 2018; Received in revised form 14 January 2019; Accepted 16 January 2019

Table 1
Predictors of current long-acting injectable antipsychotics in outpatients with schizophrenia/schizoaffective disorder.

Predictor	Regression *P*-value	Odds ratio	OR lower conf. bound	OR upper conf. bound
History of physical aggression	0.0881	1.65	0.93	2.92
Verbal aggression score	0.0117	1.27	1.06	1.53
Property aggression score	0.0350	1.24	1.02	1.50
Physical aggression score	0.0285	1.25	1.03	1.53
Sex	0.1161	1.69	0.86	3.32
Age	0.0903	1.02	0.99	1.04
European Caucasian	0.1551	0.66	0.37	1.17
Duration of illness	0.2476	1.01	0.99	1.04
Family history of psychiatric illness	0.2721	0.69	0.35	1.36
CTQ total score	0.1552	1.01	0.99	1.03
Lifetime alcohol use disorder	0.9358	1.03	0.53	2.00
Lifetime cannabis use disorder	0.1257	1.68	0.87	3.21
Suicide attempt	0.0613	1.74	0.97	3.09
Lifetime substance use disorder (not cannabis)	0.0033	2.49	1.36	4.55

OR lower and upper conf. bounds: 95% CI interval; CTQ = Childhood Trauma Questionnaire.

Table 2
Predictors of antipsychotic doses in chlorpromazine equivalents (CPZe).

	Regression *P*-value	Slope	Slope SE
History of physical aggression	0.052	+77.55	39.78
Verbal aggression score	0.006	+37.03	13.24
Property aggression score	0.311	+14.75	14.55
Physical aggression score	0.023	+33.15	14.47
Sex	0.918	+4.43	42.83
Age	0.004	+4.36	1.49
European Caucasian	0.259	+44.83	39.60
Duration of illness	0.000	+5.77	1.60
Family history of psychiatric illness	0.398	−35.73	42.22
CTQ total score	0.179	+1.57	1.17
Lifetime alcohol use disorder	0.749	+14.20	44.26
Lifetime cannabis use disorder	0.797	−11.75	45.66
Suicide attempt	0.007	+103.47	37.93
Lifetime substance use disorder (not cannabis)	0.080	+72.68	41.40

CTQ = Childhood Trauma Questionnaire.

participants were taking their prescribed antipsychotics, allowing for potential bias between participants with stable medications versus those in the process of having medications optimized for improved clinical management. Furthermore, the sample population included patients with varying durations of illness, though previous studies have indicated an increased incidence of violence in first-episode psychosis [10].

In conclusion, the purpose of the study was to provide a snapshot of the prescribed treatment for patients with a history of past violence. Further work is needed to determine how violence influences pharmacological treatment of patients with schizophrenia, and more specifically, to evaluate more effective therapies in treating and preventing violence.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.01.004.

References

[1] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76. https://doi.org/10.1093/epirev/mxn001.

[2] Hodgins S. Violent behaviour among people with schizophrenia: a framework for investigations of causes, and effective treatment, and prevention. Philos Trans R Soc Lond B Biol Sci 2008;363(1503):2505–18. https://doi.org/10.1098/rstb.2008.0034.

[3] Hodgins S, Klein S. New clinically relevant findings about violence by people with schizophrenia. Can J Psychiatry 2017;62(2):86–93. https://doi.org/10.1177/0706743716648300.

[4] Frogley C, Taylor D, Dickens G, Picchioni M. A systematic review of the evidence of clozapine's anti-aggressive effects. Int J Neuropsychopharmacol 2012;15(9):1351–71. https://doi.org/10.1017/S146114571100201X.

[5] Üçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. World Psychiatry 2008;7:58–62.

[6] Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse, and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008;8(32). https://doi.org/10.1186/1471-244X-8-32.

[7] Kishimoto T, Robenzadeh A, Leucht C, Stefan L, Watanabe K, ... Correll CU. Long-acting injectable vs. oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophrenia Bull 2014;40(1):192–213. https://doi.org/10.1093/schbul/sbs150.

[8] Pickard H, Fazel S. Substance abuse as a risk factor for violence in mental illness: some implications for forensic psychiatric practice and clinical ethics. Curr Opin Psychiatry 2013;26(4):349–54. https://doi.org/10.1097/YCO.0b013e328361e798.

[9] Sim K, Su HC, Fujii S, Yang SY, Chong MY, ... Sartorius N. High dose antipsychotic use in schizophrenia: a comparison between the 2001 and 2004 Research on East Asia Psychotropic Prescription (REAP) studies. Br J Clin Pharmacol 2008;67(1):110–7. https://doi.org/10.1111/j.1365-2125.2008.03304.x.

[10] Large MM, Nielsen O. Violence in first-episode psychosis: a systematic review and meta-analysis. Schizophr Res 2011;125:209–20. https://doi.org/10.1016/j.schres.2010.11.026.

Sarah Colbert-Kaip[a], Kevin Z. Wang[a], Ali Bani-Fatemi[a], Jermeen Baddour[a], Oluwagbenga Dada[a], Sauliha Alli[a], Clement Zai[a,b], Ariel Graff[a,b], Nathan Kolla[a,b], Vincenzo De Luca[a,b,*]

[a] *Centre for Addiction and Mental Health, 250 College St., Toronto, ON, M5T 1L8, Canada*

[b] *Department of Psychiatry, University of Toronto, Toronto, ON, M5T 1R8, Canada*

E-mail address: Vincenzo.deluca@camh.ca (V. De Luca).

[*] Corresponding author at: Group for Suicide Studies, CAMH, Canada.