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Biological Aspects of Aggression and Violence in Schizophrenia

WonKyung Cho[1], Won-Suk Shin[1], Iseul An[2,3], Minji Bang[3], Doo-Yeoun Cho[1], Sang-Hyuk Lee[1,3]

[1]Department of Clinical Pharmacology and Therapeutics, CHA Bundang Medical Center, CHA University School of Medicine, [2]Clinical Counseling Psychology Graduate School, CHA University, [3]Department of Psychiatry, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Although the majority of patients with schizophrenia are not actually violent, an increased tendency toward violent behaviors is known to be associated with schizophrenia. There are several factors to consider when identifying the subgroup of patients with schizophrenia who may commit violent or aggressive acts. Comorbidity with substance abuse is the most important clinical indicator of increased aggressive behaviors and crime rates in patients with schizophrenia. Genetic studies have proposed that polymorphisms in the promoter region of the serotonin transporter gene and in the catechol-O-methyltransferase gene are related to aggression. Neuroimaging studies have suggested that fronto-limbic dysfunction may be related to aggression or violence. By identifying specific risk factors, a more efficient treatment plan to prevent violent behavior in schizophrenia will be possible. Management of comorbid substance use disorder may help prevent violent events and overall aggression. Currently, clozapine may be the only effective antipsychotic medication to repress aggressive behavior. With the current medical field moving toward tailored medicine, it is important to identify vulnerable schizophrenia populations and provide efficient treatment.

KEY WORDS: Aggression; Violence; Schizophrenia; Neuroimaging; Antipsychotic agents.

INTRODUCTION

The prevalence of major mental disorders is higher in prisoners than in the general population [1-3]. Crime rates, especially for violent offenses, are more highly correlated with psychiatric disorders [4,5]. Moreover, prisoners with mental health issues are more likely to violate prison rules and be involved in prison infractions and violent incidents [6-9].

Individuals with schizophrenia are 4 to 7 times more likely to commit violent crimes, such as assault and homicide [4,5], and 4 to 6 times more likely to exhibit general aggressive behavior, such as verbal and physical threats [10,11], compared with the general population. Despite reports from several large cohort studies indicating an increase in violent behavior in schizophrenia [4,10,12,13], some debate remains on the association between violent behavior and the disorder. One prospective study showed no significant difference in the prevalence of violence between the general population and patients with schizophrenia [14]. Several studies have shown minimal increase in hostile behavior in schizophrenia when comorbidity for substance abuse was considered as a confounding factor [14,15]. The lack of consensus among studies is attributable to the absence of uniform variables such as substance abuse, dysfunctional childhood, and positive symptoms of psychosis. A better understanding of the confounding factors associated with violent behavior and schizophrenia is needed. Thus, if the confounding factor is modifiable, specific treatment guidelines can be drafted to manage modifiable risk in patients with schizophrenia. Furthermore, identifying specific risk factors for violence allows clinicians to diagnose those who may

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Address for correspondence: Sang-Hyuk Lee
Department of Psychiatry, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
E-mail: leesanghyuk@yahoo.com
ORCID: https://orcid.org/0000-0001-7939-3000
Doo-Yeoun Cho
Department of Clinical Pharmacology and Therapeutics, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
E-mail: dooycho@cha.ac.kr
ORCID: https://orcid.org/0000-0003-2996-1000

need closer management for early violence prevention. Predicting a patient's future conduct may cause stigmatization. Thus, structural and objective guidance measures of risk assessment, such as biological markers, are optimal.

Herein, we review the social and biological markers for violence and briefly assess the current management of patients with schizophrenia who exhibit aggressive behavior.

SCHIZOPHRENIA AND SUBSTANCE ABUSE

Current American Psychiatric Association guidelines indicate that identifying risk factors for violence and assessment of dangerousness should be part of the standard psychiatric evaluation [16]. Currently, there is no established tool to assess the risk factors of aggression in patients with schizophrenia. Previous studies have shown that substance abuse, alcohol abuse, neurological impairment, and social burdens increase risk of aggressive behavior (Table 1) [12,13,15,17-26]. Among the multiple risk factors, comorbid substance abuse and presence of positive symptoms, such as persecutory ideation, have been duplicated in several studies [13,19]. Patients with schizophrenia with comorbid substance abuse not only have more overt aggression, as measured with overt aggression scales, but have higher criminal conviction rates (odd ratio [OR] 2.35−16.1), and having more than one substance abuse exacerbates violent behavior [20].

These findings are of great clinical concern because the lifetime prevalence of comorbid substance abuse is nearly 60% in patients with schizophrenia [17,27]. Substance dependence is five times more prevalent in patients with schizophrenia than in the general population. Several hypotheses have attempted to explain the mechanism behind this phenomenon. Most antipsychotic medications block dopamine receptor D2 (D2R) that interfere with dopamine neurotransmission in the whole brain. Patients may resort to drugs of abuse to counteract the cognitive deficits induced by pre-frontal D2R blockage and compensate for the anhedonia induced by D2R blockade in the nucleus accumbens and ventral pallidum [27]. Reduction in dopamine D2 receptor has also been associated with enhanced impulsivity and reinforcement of drug use [21,27]. Overlap in genes between schizophrenia and addiction, including neuregulin 1, catechol-O-methyltransferase, v-akt murine thymoma viral oncogene homolog 1, monoamine oxidase A (MAOA), and neurexin 1 and 3, suggests a genetic vulnerability to the comorbidity. However, Fazel *et al.* [21] found that patients who had been diagnosed with substance abuse after being diagnosed with schizophrenia posed higher risk (OR 6.4) than those who had been diagnosed with substance abuse prior to being diagnosed with schizophrenia (OR 1.9). Whether a shared genetic susceptibility to substance abuse and schizophrenia increases violent behavior or schizophrenia leads to substance abuse that results in violent behavior is still in question.

The shared genetic susceptibility of substance abuse and schizophrenia suggests the correlation between aggressive behavior and schizophrenia may be due to substance abuse. Impulsivity, aggression, and substance abuse disorders share neurobiological commonalities [30]. Among criminal offenders, individuals with substance abuse have more judicial problems, including higher recidivism and more violent behavior in detention, which may possibly be due to the high impulsivity and aggressiveness found in this population [31]. Future studies should examine the correlation between the overlapping genes of substance abuse and schizophrenia with aggression.

Attributing aggressive behavior solely to schizophrenia may be misguided. Specific risk factors, such as substance abuse, should be targeted in the management of aggressive behavior exhibited by patients with schizophrenia. Treating the comorbid substance abuse may reduce violent behavior in these patients. Furthermore, future studies should be conducted to determine whether there is a clear causative relationship between comorbid substance abuse and violent behavior.

TESTOSERONE LEVEL IN SCHIZOPHRENIA

Numerous studies have shown a positive correlation between testosterone level and aggressive behavior and criminality in the general population and in patients with personality disorder [32-36]. However, no association has been found between criminal behavior and testosterone level in patients with schizophrenia [36]. In fact, one study found that low-normal testosterone level is significantly associated with more severe hostility symptoms in men with schizophrenia [37]. This finding is particularly interesting because several studies have found significantly lower levels of serum testosterone in men with schizophrenia during acute psychotic episodes but gen-

Table 1. Risk factors of violent behavior in schizophrenia

Reference	Country	Sample	Control	Risk factors	Odds ratio	Outcome (measured)
Fazel *et al.* (2009) [21]	Sweden	8,003	General population	Schizophrenia	1.2 ($p < 0.01$)	Violent crime (conviction for homicide, assault, robbery, arson, sexual offense, illegal threats, intimidation)
				Comorbid Substance abuse	4.4 ($p < 0.01$)	
Swanson *et al.* (2006) [22]	USA	1,410	Non-violent schizophrenia	Substance abuse/dependence	2.42	Minor violence (simple assault without injury or weapon use)
				Recent victimization	2.10	
				Childhood conduct problem	3.29 ($p < 0.001$)	Major violence (any assault using a weapon or resulting in injury)
				Positive PANSS score	2.71 ($p < 0.01$)	
				Substance use/abuse	2.10	
				Recent non-violent victimization	2.27 ($p < 0.05$)	
Wallace *et al.* (2004) [13]	Australia	2,681	Community population	Schizophrenia	2.5 ($p < 0.001$)	Criminal convictions due to violent offenses (violence resulting in serious injury and homicide)
				Comorbid substance use	19.1 ($p < 0.001$)	
Koen *et al.* (2004) [23]	South Africa	70	Non-violent schizophrenia	Delusions of control	3.7	History of physical violence reported by family or by hospital staff
				Use of cannabis/alcohol	6.89	
Cantor-Graae *et al.* (2001) [17]	Sweden	87	Schizophrenia without criminal offence	History of substance abuse	50.0% vs. 11.1% in crime rate ($X^2 = 15.7$) ($p < 0.001$)	Criminal convictions
Arseneault *et al.* (2000) [12]	New Zealand	39	Cohort population	Schizophrenia	2.5	Court convictions for violence
				Comorbid alcohol dependence	8.3	
				Comorbid marijuana dependence	18.4	
Räsänen *et al.* (1998) [18]	Finland	76	Cohort population	Schizophrenia	3.6 ($p < 0.01$)	Violent crime records (homicide, assault, robbery, arson, violation of domestic peace)
				Comorbid alcohol abuse	25.2 ($p < 0.01$)	
Cuffel *et al.* (1994) [20]	USA	103	Non-violent schizophrenia	Alcohol or marijuana use	2.35	Clinical records of violence (including verbal/nonverbal threats, physical assaults, using a weapon)
				Polysubstance use	12.56 ($p < 0.01$)	
Caqueo-Urízar *et al.* (2016) [24]	Chile, Bolivia, Peru	253	OAS < 7 (non-violent)	Mean number of hospitalization in the last 3 years	1.40 ($p < 0.001$)	Overt aggression scale
Fresán *et al.* (2007) [25]	Mexico	102	OAS < 7 (non-violent)	Novelty seeking in TCI scale[a]	6.12 ($p = 0.001$)	Overt aggression scale
				Lack of Cooperativeness[b]	11.07 ($p < 0.001$)	
Wong *et al.* (1997) [26]	Australia	39	Non-repetitive violent offenders with schizophrenia	Childhood conduct problems	16.7 ($p < 0.01$)	Previous history of a violent offence (i.e., manslaughter or murder)
				Impulsive suicide attempt	6.7 ($p = 0.02$)	

PANSS, positive and negative syndrome scale; OAS, overt aggression scale; TCI, temperament and character inventory.
[a]Novelty seeking measures tendency of impulsiveness and quick loss of temper; [b]Lack of cooperativeness accounts for self-centered aggression and hostility.

erally not during the maintenance phase [38-40]. The above findings suggest an association between acute psychotic episodes and lower testosterone level. However, another study showed no correlation between testosterone level and degree or type of aggression [41].

Many studies have attributed the low levels of testosterone found in patients with schizophrenia to the chronic use of antipsychotics [36]. Antipsychotics increase the risk of diabetes, and diabetes is associated with low testosterone concentrations [42,43]. In the short-term, antipsychotics, such as haloperidol, suppress serum testosterone [44]. However low testosterone is found in antipsychotic-naive patients with schizophrenia, suggesting a disease component to reduced testosterone levels [45]. Further study is needed to assess the negative correlation between testosterone and aggression in newly diagnosed schizophrenia to confound for chronic antipsychotic use.

GENETIC MARKERS OF AGGRESSION IN SCHIZOPHRENIA

Genetic background is estimated to account for 50% of human aggression [46]. Numerous studies have investigated the gene responsible for aggression in schizophrenia. The genes responsible for regulating the serotonergic and catecholaminergic systems are considered key genes. Several studies have shown reduction in cerebrospinal fluid levels of serotonin metabolite 5-hydroxyindoleacetic acid in aggressive males with deviant behavior [47-49]. However, genetic studies on serotonin transporter have identified no significant association between aggression and schizophrenia [50,51]. Catechol-O-methyltransferase and MAOA genes encoding for enzymes responsible for catabolism of catecholamine have also been explored. Catechol-O-methyltransferase and MAOA knockout mice showed elevated aggression [52]. Studies have shown varied results, partly due to different sample populations and varying measures of aggression (Table 2) [23,50,51,53-70]. The most recent meta-analysis found no association between any polymorphism and aggression and did not provide any evidence supporting the use of genetic markers for risk prediction and management of aggression in schizophrenia patients [71]. However, this analysis cannot be considered conclusive because sample sizes used in the review were small. Moreover, a complex behavior such as aggression is likely to be mediated by complex interaction among many genes, as opposed to what single polymorphism studies have been trying to pinpoint. Future studies examining the genetic association between aggression and schizophrenia using alternative study designs are needed.

NEUROIMAGING FINDINGS REGARDING AGGRESSION AND VIOLENCE IN SCHIZOPHRENIA

Abnormalities in various parts of the brain have been associated with increased aggression with no single brain area acting as a key region. Hoptman and Antonius [72] found that frontal and temporal abnormalities were associated with aggression in schizophrenia. Several other studies have found that different brain regions influence violence in schizophrenia (Table 3) [26,73-86]. Aggression control is multifaceted, and dysfunction in functional connectivity between the amygdala and prefrontal cortex tends to predict higher levels of aggression [73,74]. The most consistent findings from the structural studies were reduced volumes of the hippocampus and the frontal lobe (in particular, the orbitofrontal and anterior cingulate cortex) in patients with schizophrenia with a history of violence or higher aggression scores. These findings suggest that dysfunctions of fronto-limbic regions in schizophrenia can be associated with aggression or violence. However, the neuroimaging findings of aggression and violence were methodologically heterogeneous, with four particular areas of concern: different definitions of violence, region of interest versus whole-brain studies, small subject samples, and group comparisons in a heterogeneous diagnostic category [87].

MANAGEMENT OF AGGRESSION IN SCHIZOPHRENIA

Antipsychotic treatment significantly reduces aggression in patients with schizophrenia [88]. However, who should receive treatment and which drugs should be administered are still under debate. Because no specific biomarkers or pharmacogenetic tests are available to guide treatment choice, treatment is still chosen based on broad guidelines and is not personalized.

The overwhelming opinion in the past was that atypical antipsychotics, such as clozapine, risperidone, quetia-

Table 2. Genetic factors of aggression in schizophrenia

Reference	Country	Sample	Control	Outcome (measured)	Gene	Main findings
Tosato *et al.* (2011) [54]	Italy	80	Non-violent SCZ (OAS < 22, ≤ 1 aggressive episode)	OAS Number of episodes of aggression (6-year f/u)	Val158Met polymorphism of COMT	Met/Met[a] homozygous associated with higher aggression than Val/Val
Kim *et al.* (2008) [55]	South Korea	574 (165 SCZ)	Non-violent SCZ	Repeated violence resulting in confinement Documented serious assault to others		No significant associationbetween the aggressive behavior and COMT Val158Met polymorphism
Han *et al.* (2006) [56]	South Korea	132		OAS		Met allele associated with increased aggression in SCZ
Park *et al.* (2002) [57]	South Korea	103		Documented assaults (hospital records and official arrest records)		No association between COMT gene and violence in schizophrenia
Liou *et al.* (2001) [58]	China	198	Non-violent SCZ	Physical aggression against others (medical chart review)		No significant difference in allele frequencies btw violent and non-violent SCZ
Jones *et al.* (2001) [53]	UK	180		OAS		Val/Val homozygotes associated with higher aggression in SCZ (vs. other genotypes)
Lachman *et al.* (1998) [59]	USA	55	Non-violent SCZ	Documented physical assault to others (hospital records and official arrest records)		Higher frequency of Met/Met homozygous found in violent behavior SCZ
Guan *et al.* (2014) [60]	China	579	Non-violent SCZ (300)	Modified OAS	Val66Met polymorphism of BDNF gene	Val66Met polymorphism not associated with aggressive behavior
Chung *et al.* (2010) [61]	South Korea	101	Non-homicide SCZ	Homicide conviction		Val66Met polymorphism not associated with aggressiveness in SCZ
Koh *et al.* (2011) [62]	South Korea	232 (99 SCZ)	Healthy Control Non-homicide violent SCZ	Homicide conviction Non-homicide violent conviction	Val158Met polymorphism of COMT gene TPH1 A218C	No difference in distribution of Val158Met polymorphism between criminal SCZ (vs. healthy control) TPH1-CC recessive associated with homicidal SCZ (vs. A-carrier genotype)
Gu *et al.* (2009) [63]	China	584	Healthy Control Non-violent SCZ	Documented homicide or malicious injury	COMT gene SNP (rs4680-rs165599-rs737865) Haplotype A-A-G (vs. GGA)	No association between individual SNPs and violent behavior Higher frequency of haplotype A-A-G associated with violent behavior
Hong *et al.* (2008) [64]	South Korea	193	Non-violent SCZ	Homicide conviction	Val158Met polymorphism of COMT gene Ala72Ser SNP of COMT gene	No difference in distribution of Val158Met polymorphism between violent and non-violent SCZ L allele (low COMT activity) of Ala72Ser more frequent in violent SCZ
Koen *et al.* (2004) [23]	South Africa	70	Non-violent SCZ	History of violence reported by family or hospital staff	Val158Met polymorphism of COMT MAO A, MAO B polymorphism	COMT or MAO A polymorphism not associated with violence in SCZ
Zammit *et al.* (2004) [65]	UK	346 150 (COMT)		OAS		No association between MAO A, MAO B and COMT polymorphisms and aggressive behavior
Strous *et al.* (2003) [66]	Israel	122		Life history of aggression scale		Met/Met homozygous associated with higher aggression than Val No association between MAO A and aggression

Table 2. Continued

Reference	Country	Sample	Control	Outcome (measured)	Gene	Main findings
Kim *et al.* (2009) [67]	South Korea	103	Non-violent SCZ	≥ 2 violent acts leading to confinement	5-HTTLPR	No difference in the distribution of genotype/allele between violent and non-violent SCZ-frequency of short allele associated with high angry temperament subscale score in aggressive patients
Fresan *et al.* (2007) [68]	Mexico	71	Non-violent SCZ (OAS ≤ 6)	OAS	DRD4 polymorphism (7R allele)	Higher prevalence of 7R variant of DRD4 gene in aggressive SCZ
					MAO-A polymorphism	No association between the MAO-A gene and aggressive behavior
Han *et al.* (2004) [51]	South Korea	168		OAS	Val158Met polymorphism of COMT	Met homozygote associated with increased aggression in SCZ (especially in aggression against others)
					5-HTTPR	L(long) allele associated with higher all episode of aggression
Nolan *et al.* (2000) [50]	USA	84	Non-violent SCZ	History of ≥ 2 assaults on others	MAO-A polymorphism 5-HTT polymorphism	5-HTT or MAO-A polymorphism not associated with violence in SCZ
Kotler *et al.* (1999) [69]	Israel	92	Non-violent SCZ	Imprisoned for homicide	Val158Met polymorphism of COMT	Higher frequency of Met/Met found in violent SCZ (vs. non-violent)
					D4DR	No association between violent SCZ with D4DR, 5-HTTLPR polymorphism
					5-HTTLPR	
Tsai *et al.* (1999) [70]	Taiwan	186	Non-violent SCZ	Physical aggression against others (hospital records)	Allelic variant C267T of 5-HT6 gene	No significant difference in genotype/allele frequencies between SCZ with or without aggressive behaviors

SCZ, schizophrenia; OAS, overt aggression scale; COMT, catechol-O-methyltransferase; BDNF, brain derived neurotrophic factor; TPH1-CC, tryptophan hydroxylase-1 A218C gene for 5-HT metabolism; MAO, monoamine oxidase; 5-HTTLPR, serotonin transporter-linked polymorphic region; 5-HTT, serotonin transporter; D4DR, dopamine D4 exon III repeat length polymorphism; 5-HT6, serotonin type 6 receptor.

[a]Met is the low activity allele.

Table 3. Neuroimaging studies on aggression in schizophrenia

Reference	Country	Sample	Control	Imaging study	Outcome (measured)	Main findings
Kumari *et al.* (2009) [75]	UK	38 (24 SCZ)	Healthy control Non-violent SCZ	Structural MRI	Record of serious physical fatal or near fatal violence (≥ 5 in Gunn and Robertson scale)	↑ Impulsiveness in violent SCZ which correlated negatively with ↓ hippocampal volume (vs. correlated with ↓ OFC grey matter volume in non-violent SCZ and healthy control)
Puri *et al.* (2008) [76]	UK	26	Non-violent SCZ		History of violent offence (homicide, attempted murder, grave bodily harm)	Bilateral ↓ in cerebellar and supramarginal gyrus-associated cerebral cortical grey matter (vs. non-violent SCZ)
Hoptman *et al.* (2006) [77]	USA	49			Total aggression severity score-derived from OAS	↑ Left caudate volume with higher total aggression score
Rüsch *et al.* (2008) [78]	Italy	110 (55 SCZ)	Healthy controls		Modified OAS	Bilaterally ↑ inferior frontal white matter volume associated with suicidality and self-aggression in schizophrenia
Hoptman *et al.* (2005) [79]	USA	49			OAS	↑ Left OFC gray matter volumes associated with aggression ↑ Left than right OFC white matter volumes associated with comorbid substance use disorder
Barkataki *et al.* (2006) [80]	UK	43 (30 SCZ)	Healthy Control Non-violent SCZ		History of detainment for violence (e.g., homicide, attempted murder, wounding)	↓ Whole brain volume (vs. non-violent SCZ and healthy control) ↓ Hippocampal volume (vs. healthy control)
Hoptman *et al.* (2002) [81]	USA	14		Axial diffusion tensor MRI	Buss Durkee Hostility Inventory Life History of Aggression Self-report	Inferior frontal white matter microstructure is associated with impulsivity and aggression
Kumari *et al.* (2009) [82]	UK	53 (26 SCZ)	Healthy control Non-violent SCZ	fMRI (shock threat)	History of serious violence (≥ 5 in Gunn and Robertson scale)	Exaggerated thalamic-striatal activity to later threat periods (vs. non-violent SCZ and healthy control)
Dolan *et al.* (2009) [73]	UK	24	Low Psychopathy SCZ	fMRI (facial affect series recognition task)	High psychopathy score (> 18 in PCL:SV)	↓ BOLD response in right amygdala-prefrontal cue when presented with fearful cue
Hoptman *et al.* (2010) [74]	USA	46 (21 SCZ)	Healthy controls	fMRI (voxelwise FC analysis)	Buss Perry aggression questionnaire	↓ Functional connectivity between amygdala and prefrontal cortex (vs. healthy control)(lower functional connectivity associated with higher self-reported aggression in SCZ)
Kumari *et al.* (2006) [83]	England	48 (25 SCZ)	Healthy control Non-violent SCZ	fMRI (working memory load task)	History of serious violence according to clinical and criminal records (≥ 4 in Gunn and Robertson scale)	Bilateral activation deficit in the frontal lobe and precuneus compared to the healthy controlActivation deficit in the right inferior parietal region when compared to the NVS ↓ Right inferior parietal region (vs. non-violent SCZ).
Joyal *et al.* (2007) [84]	Canada	48 (36 SCZ)	Healthy control Non-criminal SCZ	fMRI (go/no-go task)	Homicide offense	↓ Activation of orbital, basal regions of PFC (vs. control and non-criminal SCZ) ↑ Activation in motor, premotor anterior cingulate cortex (vs. non-criminal SCZ)
Wong *et al.* (1997) [26]	Australia	39	NRVOs with SCZ	MRI, FDG-PET, EEG	Previous history of violent offence (i.e., manslaughter or murder)	Asymmetrical gyral pattern in temporo-parietal region in RVOs (Absent in NRVOs) Not associated with hypometabolism in this area in PET EEG abnormality localized to temporal side in RVOs
Wong *et al.* (1997) [85]	Australia	31 SCZ	NRVOs with SCZ	FDG-PET	Previous history of violent offence (i.e., manslaughter or murder)	↓ FDG uptake in left anterior-inferior temporal regions (vs. bilateral reduction in NRVOs)
Spalletta *et al.* (2001) [86]	Italy	15 SCZ	Non-violent SCZ	SPECT[a]	Hospital records of aggression	↓ Prefrontal rCBF under neuropsychological stress (NOT at resting state)

SCZ, schizophrenia; MRI, magnetic resonance imaging; OAS, overt aggression scale; OFC, orbitofrontal cortex; PCL:SV, psychopathy check list: Screening version; BOLD, blood oxygen level-dependent; NVS, non violent schizophrenia; FDG-PET, fluorodeoxyglucose positron emission tomography; EEG, electroencephalogram; RVOs, repetitive violent offenders; NRVOs, non-repetitive violent offenders; SPECT, single photon emission computed tomography; rCBF, regional cerebral blood flow.

pine, and ziprasidone, were the most effective drugs in the treatment of patients with aggression and violent behavior [89-91]. However, two large double-blind trials found no advantage to the use of second-generation antipsychotics in treating chronic schizophrenia, thereby questioning its true effectiveness [53,92]. There is still mixed evidence showing clozapine and olanzapine are more effective than haloperidol; however, the same study shows perphenazine, a first-generation drug, is more effective than haloperidol as well [93]. Another study using data from the Clinical Antipsychotic Trials of Intervention Effectiveness project also did not find any advantage to the use of second-generation antipsychotics in violence risk reduction, compared with perphenazine [88]. However, that study did not include treatment response to clozapine, the most effective drug in reducing aggression in patients with schizophrenia [90,94-96].

Although mixed results question the use of atypical antipsychotics as first-line treatment for schizophrenia, clozapine may still be the most effective drug in reducing aggression. The exact mechanism of clozapine's anti-aggressive effect is not yet understood, but the effect seems to be independent of the sedative and antipsychotic effect of the drug [97]. Moreover, little improvement has been made in antipsychotics since clozapine in the 1950s. Expert consensus guideline [98] has recommended the use of clozapine and risperidone as first-line treatments for chronic aggression. Despite this recommendation, clozapine is rarely used as a first-line treatment because of its hematological side effects. Burdensome full blood count monitoring is required throughout the treatment. Such tedious monitoring may increase the already high non-adherence seen in schizophrenia [99]. When administering clozapine, interventions including medication education, psychoeducation, and motivational interviewing techniques should be utilized to increase compliance [100].

Treatment of substance use disorder may also be helpful in managing aggressive behavior in patients with schizophrenia. Second-generation antipsychotics, such as clozapine and risperidone, have been found to reduce the drive to self-medicate the negative symptoms [101] and not to have the side effects of typical antipsychotics, allowing for better control for substance use. Moreover, low striatal dopamine is associated with neuroleptic-induced dysphoria and with vulnerability to addiction. Choosing an antipsychotic medication that is a weak dopamine D2 blocker will avoid further compromising dopamine striatal functioning, thus reducing the possibility of addictive behavior [102].

CONCLUSION

Identification of risk factors should provide a basis for a management plan and not a means of labeling a patient as pre-delinquent, especially because aggression significantly decreases under treatment [88]. Despite efforts to find biological, genetic markers associated with aggression in schizophrenia, no consistent findings have been established to explain violent and aggressive behavior in schizophrenia. Further study is needed before any discussion on using such markers to predict patient behavior.

Among multiple risk factors, comorbid substance abuse has repeatedly been found to be associated with aggressive behavior. Patients with schizophrenia without comorbid substance abuse have only a slight increased risk of violent crime compared with the general population, suggesting that substance abuse plays a mediating role. Whether aggressive behavior in schizophrenia can solely be attributed to comorbid substance abuse or whether a specific underlying gene results in both the aggression and comorbid substance abuse in schizophrenia requires further study. Nonetheless, treating the comorbid substance abuse is necessary in managing violent behavior in patients with schizophrenia.

With the increasing perception that patients undergoing psychiatric treatment are dangerous, precariously identifying risk factors can exacerbate this notion.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Study design: WonKyung Cho, Won-Suk Shin, Minji Bang, Doo-Yeoun Cho, Sang-Hyuk Lee. Data review, interpretation and manuscript preparation: WonKyung Cho, Won-Suk Shin, Minji Bang, Doo-Yeoun Cho, Sang-Hyuk Lee. Writing—original draft: WonKyung Cho, Won-Suk Shin, Doo-Yeoun Cho, Sang-Hyuk Lee. Writing—review & editing: Iseul An, Doo-Yeoun Cho, Sang-Hyuk Lee. Supervision: Doo-Yeoun Cho, Sang-Hyuk Lee.

■ ORCID

WonKyung Cho https://orcid.org/0000-0002-0290-8667
Won-Suk Shin https://orcid.org/0000-0002-6163-5726
Iseul An https://orcid.org/0000-0003-4008-0730
Minji Bang https://orcid.org/0000-0002-1669-4014
Doo-Yeoun Cho https://orcid.org/0000-0003-2996-1000
Sang-Hyuk Lee https://orcid.org/0000-0001-7939-3000

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