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Pharmacological interventions to reduce violence in patients with schizophrenia in forensic psychiatry

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Review

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Abstract

Background. The purpose was to systematically investigate which pharmacological strategies are effective to reduce the risk of violence among patients with Schizophrenia Spectrum Disorders (SSD) in forensic settings.

Methods. For this systematic review six electronic data bases were searched. Two researchers independently screened the 6,003 abstracts resulting in 143 potential papers. These were then analyzed in detail by two independent researchers. Of these, 133 were excluded for various reasons leaving 10 articles in the present review.

Results. Of the 10 articles included, five were merely observational, and three were pre-post studies without controls. One study applied a matched case-control design and one was a non-randomized controlled trial. Clozapine was investigated most frequently, followed by olanzapine and risperidone. Often, outcome measures were specific to the study and sample sizes were small. Frequently, relevant methodological information was missing. Due to heterogeneous study designs and outcomes meta-analytic methods could not be applied.

Conclusion. Due to substantial methodological limitations it is difficult to draw any firm conclusions about the most effective pharmacological strategies to reduce the risk of violence in patents with SSD in forensic psychiatry settings. Studies applying more rigorous methods regarding case-definition, outcome measures, sample sizes, and study designs are urgently needed.

Introduction

The World Health Organization (WHO), in its report on violence and health defined violence as "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation".[1] In this paper, we used the WHO definition of violence as orientation, but did not focus on violence against oneself.

There are links between a range of mental disorders and the risk of violence. A systematic review and meta-analysis[2] on 20 original studies demonstrated a clear association between schizophrenia, substance use disorders and violence. They reported an OR of 2.1 (95% CI 1.7–2.7) for those with schizophrenia only compared to the general public, with that risk rising markedly when substance use disorder was also present (OR 8.9, 95% CI 5.4–14.7).

While the overall contribution of violent offences committed by patients with schizophrenia to society's general level of violence is very small, it is nevertheless true that patients' violence presents a clear threat to staff, other patients and the public around them.[3] For example up to 83% of staff in general psychiatric institutions frequently experienced verbal violence,[4] while up to 50% of staff reported that they were frequently threatened by their patients.

Some authors used linkage of population-based registers to analyze within individuals if the onset of antipsychotics, mood stabilizers, or other psychotropic medications reduced violence.[5–7] They showed that antipsychotics reduced the frequency of violent crime and reoffending after prison release. This within-individual study design can account for factors which remain stable within the same patient (eg, sex, education). Since pharmacoepidemiologic studies can neither consider all time-varying cofounders nor reverse causality, this study design cannot assert causal effects. For example, factors that motivate individuals to use medications may be the same factors which influence them to not reoffend. Further, the prescription of some medication could be

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accompanied with more regular contact with health-care staff or support from family. Such pharmacoepidemiologic studies must rely on data available in population-based registers such as prison release or conviction as proxies for violence, but do not give any information about violence in everyday life.[5]

Violence reduction is among the goals of treatment in general and emergency psychiatric care settings as well as in forensic psychiatry, where both pharmacological and non-pharmacological strategies are used.[4,8,9] Forensic psychiatrists rely to a large extent on research conducted in general psychiatry settings[8,10] to guide their practice. However, it is unclear if the therapeutic interventions used to manage and prevent violence in general psychiatry settings are effective in forensic settings. Some argue that the interventions used to manage violence in forensic psychiatry should be similar to those used in general psychiatry.[9] There are however differences. Firstly, most if not all patients in forensic settings have a history of severe violence.[11] Secondly, in forensic settings poor symptom control can more easily lead to extreme violence,[9] that can then influence broader prescribing habits, leading for example to more frequent use of antipsychotic polypharmacy and high-dose antipsychotic prescribing in forensic settings.[12] A third important difference is that patients in forensic settings are almost universally under mandatory care, and therefore the procedures for the prescription and administration of psychotropic drugs used in the general mental health settings do not necessarily apply. For instance, at least in some countries, the forcible administration of psychotropic medications to forensic patients is ordinarily allowed, in case they do not comply with medication compliance.[13]

The extent to which it is possible to reduce violence in patients with schizophrenia using psychiatric medicines has already been studied in non-forensic settings several times.[14,15] In contrast, studies to evaluate the effectiveness of medicines to reduce violence in forensic psychiatry settings are rare. Among the reasons for this shortcoming are the legal and ethical frameworks in some countries that limit the extent to which pharmacological research can be conducted in detained patients.[11] In contrast, it can be argued that patients who have been violent and are detained in hospital for treatment to address that risk in fact are the patients with the greatest need to establish the evidence for effective treatment.

Research question

The aim of this systematic review was to investigate which pharmacological strategies are effective to reduce the risk of violence by patients with Schizophrenia Spectrum Disorders (SSD) in forensic settings.

Methods

Data collection and analysis

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA[16]). The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews on July 1st, 2018 (registration number CRD42019146933).

Medline, PsycINFO, and Psyndex Lit & AV via Ovid search engine, CINAHL via EBSCOhost, Scopus, Web of Science (Core Collection) and EMBASE were used. We decided to design an explicitly broad search query, in order to identify the full range of possible pharmacological interventions (search terms listed in Appendix). The EMBASE search was performed on August 24th, 2018. All other searches were performed on August 2nd, 2018. After duplicates were removed (tools in the search engines assisted by the EndNote deduplication function) 5,338 articles remained for closer scrutiny. Since the very large number of papers took more than one year to screen, an additional search was performed (EMBASE on November 15th, 2019; other data bases on November 12th, 2019) for the period since the first search.

This resulted in 6,003 articles (Figure 1) that were scrutinized independently by two researchers applying the following inclusion criteria.

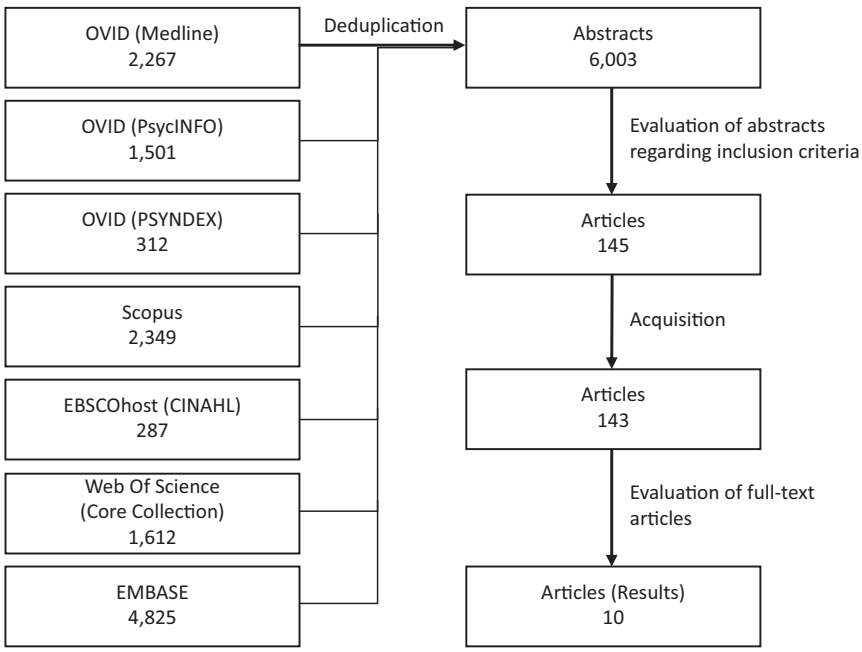

Figure 1. Flow diagram of the literature search.

- patients aged 18 years or older (those below 18 years were excluded because of differing legislation in many countries);
- patients suffering from SSD;
- use of psychotropic and other medications to manage violence;
- randomized controlled trials (RCT) or observational studies performed in forensic psychiatric in- or outpatient settings;
- outcome measures included a reduction of violence;
- published in peer reviewed journals;
- published after 1990.

Of the 6,003 abstracts identified, 5,858 were screened out leaving 145 papers, one of which was later excluded as it was in Croatian, while another could not be acquired despite numerous attempts.

The remaining 143 articles were subject to an in-depth analysis by two researchers and suitable outcome measures extracted. Differences in violent incidents or violence severity levels were considered as primary outcomes. Disagreements were resolved consensually. Checking the references yielded no additional relevant papers. The in-depth analysis excluded further papers for the following reasons:

- Two papers were duplicates;
- 11 investigated a different topic, for example, the genetic risk for violence;
- 32 papers were in ineligible formats such as reviews, meta-analyses, or meeting abstracts;
- 28 were either not concerned with a pharmacological intervention or did not analyze the effects;
- 14 used qualitative study designs (eg, content analyses of texts) or described case series;
- 11 studies were not in a forensic setting;
- 21 articles had no suitable violence outcome measure (eg, psychometric measures about cognitive functioning or psychotic symptoms);
- 12 articles either included other diagnoses or did not discriminate between different diagnoses;
- Two articles failed to meet the age criterion.

This yielded a final total of 10 articles for inclusion in the systematic review.

Coding outcomes and study quality evaluation

The GRADE methodology (Grades of Recommendation, Assessment, Development, and Evaluation) was used to assess the quality of the evidence of the final 10 articles.[17] Two authors (RS, AR) independently rated each article using the following criteria while differences in the raters' opinions were resolved by discussion.

The GRADE-criteria include:

- risk of bias;
- inconsistency;
- indirectness;
- imprecision;
- and publication bias.

The overall quality of evidence from a study can be rated between very high for RCT to very low for observational studies.

For most articles included in this review it was possible to calculate the effect size on violence for the intervention tested using Cohen's *D*.

Results

A summary of the studies included in this systematic review is given in Table 1. Three studies were conducted in the United States, two in Canada, two in the United Kingdom, two in Germany, and one in Croatia. Half of all studies were exclusively observational, while three were pre-post studies with no other control group. One paper reported a matched case-control design and one a non-RCT. Clozapine was investigated most frequently,[18,23,25] followed by oral risperidone[19,21], and oral olanzapine[10,11]. Ruzic et al[22] compared the effects of Second Generation Antipsychotics (SGAs) versus First Generation Antipsychotics (FGAs), and Tavernor et al[24] analyzed the effects of different antipsychotic doses in chlorpromazine-equivalents. One study[20] tested the impact of omega-3 fatty acid supplements.

Ruzic et al[22] analyzed if patients with schizophrenia (n = 98) on forensic psychiatric wards who received SGAs were less violent, measured on the Aggressiveness Questionnaire (AG-87) than those treated with FGAs. Contrary to their hypothesis, the authors found no significant effect of antipsychotic type on violence scores as measured by patient self-ratings on the AG-87.[22] The main limitation of this study was its observational non-randomized nature. There was also no information on blinding of either the subjects or assessors to the treatment regimens administered (Table 2).

Stoner et al[23] retrospectively evaluated differences in time to release for 67 forensic psychiatry patients admitted at the Missouri Psychiatric Rehabilitation Center for inpatient treatment suffering from schizophrenia (n = 46) and schizoaffective disorder (n = 21) treated either with oral haloperidol (n = 46) or clozapine (n = 21). The authors analyzed the length of time from starting treatment until patients were conditionally discharged from the forensic unit that served as a proxy for the level of violence that the patients presented, and thus their perceived risk of violence. Those on haloperidol were released on average 4.9 years after starting treatment, while on clozapine it was 3.6 years, that was not significantly different. There was a significant difference in seclusion rates between the two groups (56.6% for haloperidol versus 14.3% for clozapine, $P = 0.032$). Revocation of conditional release after discharge was used as a final proxy marker of violence risk. Patients on clozapine were less frequently subject to revocation compared to those on haloperidol (0% versus 59.0%; $P = .046$). The main limitation of this study was its observational, non-randomized design.

Balbuena et al[18] retrospectively extracted data from the charts of forensic patients (n = 65) who received clozapine for at least 6 weeks during their treatment in a forensic institution. A cohort of forensic patients (n = 33) who never received clozapine served as control group. A high proportion of the study sample (about a quarter) was serving a life sentence. For the 12-month period after treatment, the mean count of offences was 0.62 for the clozapine group and 1.37 for the non-clozapine group. A negative binomial regression model showed that drug (ie, clozapine versus non-clozapine) significantly predicted the mean institutional offense rate, even when adjusting for other variables. Compared to those who were on clozapine, those who did not receive it had a higher post-treatment institutional offense rate (Incidence Rate Ratio = 2.22, $P = 0.02$). Again, this study was only observational.

Ebrahim et al[25] retrospectively analyzed the effects of clozapine on violence and other patient outcomes in 27 chronically psychotic and violent forensic patients treated in a maximum-security forensic psychiatric state hospital in California, USA. Assessments were performed twice, once before starting treatment with clozapine, and after 6 months. The authors looked at the average number of

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Table 1. Description of the Papers Included (Language: EN—English, FR—French, DE—German)

1st Author, Year	Language	Country	Setting	Intervention	Measure	Design
Balbuena[18]	EN	Canada	Forensic psychiatric hospital	Clozapine	Number of offenses post-treatment.	Observational study
Beck[19]	EN	USA	Three forensic wards of a state mental hospital	Risperidone 6 mg/day (versus conventional. Antipsychotics)	Frequency of incidents.	Matched case-control trial
Brosseau[20]	FR	Canada	Psychiatric hospital for offenders ruled not-guilty by mental disorder	Supplement of omega-3 fatty acids	Number of administration of PRN medication in case of agitation.	Non-RCT
Ebrahim[25]	EN	USA	State hospital, patients committed under a provision of state penal code	Clozapine	Days in restraint within 6mo on clozapine medication.	Pre-post study, no controls
Gibbon[21]	EN	UK	Four UK high-secure psychiatric hospitals	Risperidone long-acting injection	Number of "adverse incidents" (aggression, violence, self-harm).	Observational study
Ružić[22]	EN	Croatia	Two forensic psychiatric institutions	Typical antipsychotics versus atypical antipsychotics	Aggressiveness Questionnaire (AG-87):—aggressiveness—physical manifest aggressiveness—physical latent aggressiveness.	Observational study
Stadtland[11]	DE	Germany	Several forensic psychiatric institutions.	Olanzapine	ILRV	Pre-post study, no controls
Stadtland[10]	DE	Germany	Several forensic psychiatric institutions	Olanzapine	Frequency of incidents: violence (general).	Pre-post study, no controls
Stoner[23]	EN	USA	Patients in a Psychiatric Rehabilitation Center, hospitalized due to forensic court commitment	Clozapine versus haloperidol / typical antipsychotics	Documented physically aggressive incidents leading to restraint /seclusion.	Observational study
Tavernor[24]	EN	UK	Maximum security hospital	High dose (>1400 mg chlorpromazine equivalent) versus low-dose (<1000 mg chlorpromazine equivalent) per day	SDAS: aggression general/peak	Observational study

Abbreviations: ILRV, Integrierte Liste der Risikovariablen; SDAS, Social Dysfunction and Aggression Scale.

days in restraint and the level of patient privileges during the 6-month follow up evaluated according to the hospital's five-level rating system. The authors found that patients spent on average 12.4 days under restraint due to violence before starting treatment with clozapine, while this dropped to zero during the 6 months after initiating clozapine ($P < .01$). Patient privileges also improved. Before starting clozapine 18 patients (70.3%) were on the lowest level of privilege, while after 6 months of clozapine 19 patients improved by at least two levels. Unfortunately, the authors did not use a control group in this retrospective observational study.

Tavernor et al[24] explored the link between the dose of antipsychotic medications and violence risk in forensic patients. The study employed a case-control design. Cases were defined as forensic patients with schizophrenia or schizoaffective disorder who received a daily antipsychotic dose of 1,400 mg chlorpromazine-equivalents or more, while controls had a daily dose of less than 1,400 mg. The controls were matched to cases for age, sex, length of illness, Mental Health Act classification, history of violence, and ward dependency level. Patients were assessed using the Social Dysfunction and Aggression Scale (SDAS).[26] Cases scored significantly higher on the general level of violence (most severe act of violence over the past year, 10.3 and 6.4, respectively, $t = 2.1$, $P = .044$) and the peak level of violence (most severe act of violence over the past month, 18.0 and 12.2, $t = 2.4$, $P = .019$) on the SDAS compared to controls. The main limitations of this study were again its observational design, and the lack of information about why patients were on higher doses than others at study outset.

In a retrospective study Stadtland and Nedopil[11] investigated the effects of oral Olanzapine in 23 forensic patients treated in several German forensic hospitals. The patients received olanzapine with a mean dose of 15.4 mg/day and a range of 5 to 30 mg/day for at least 12 weeks. Patients were evaluated twice, once before and once after 12 weeks of olanzapine treatment, using the 7-item clinical subset of the Integrated List of Risk Variables' (ILRV).[27] After 12 weeks of olanzapine, patients' average ILRV score improved by an average of over two points ($P < .001$). However, due to the lack of a control group and blinding, the quality of evidence from this study is considered to be very low.

In a second study, Stadtland et al[10] looked again at the effects of 12 weeks of oral olanzapine on violent behavior in 35 forensic

Table 2. Effects of Pharmacological Trials

Publication	Intervention	Outcome	Control Condition (Treatment As Usual, TAU)	Intervention Condition	Absolute Effect	Relative Effect	Effect Size (Cohen's d)	Persons in Control Group (Studies)	Persons in Intervention Group (Studies)	Quality of the Evidence (GRADE)	Comments
Balbuena[18]	Effect of clozapine	Offense rate post-treatment. Number of offenses				IRR = 2.22 [1.11; 4.11]	n/a	33 (1 study)	65 (1 study)	⊕◯◯◯ Very low[a,b,c,d,e]	
Beck[19]	Effects of risperidone (6 mg target dose) versus typical neuroleptics	Frequency of aggressive incidents	n/a	n/a	n/a		n/a	10 (1 study)	10 (1 study)	⊕◯◯◯ Very low[a,b,c,d,f]	No significant effect ($P > .05$)
Brosseau[20]	Effects of omega-3 fatty acid supplements	Agitation. Frequency of PRN medication in case of agitation	mean = 32.7; SD = n/a	mean = 22.6; SD = n/a	MD = 10.1; SE = n/a		1.172	No	12 (1 study)	⊕◯◯◯ Very low[a,c,d,g]	
Ebrahim[25]	Effects of clozapine	Aggressive behavior. Days in restraint within 6mo on clozapine medication.	mean = 12.4; SD = 28.7	mean = 0; SD = 0	MD = 12.4; SE = 5.523		.611	No	27 (1 study)	⊕◯◯◯ Very low[a,c,d]	
Gibbon[21]	Effect of Risperidone Long-acting Injection (RLAI)	Aggressive behavior Decrease of "adverse incidents" (aggression, violence, self-harm)				OR = 0.75	.162	No	118 (1 study)	⊕◯◯◯ Very low[a,b,c,d]	
Ružić[22]	Effect of typical versus atypical antipsychotics	Aggression. Aggressiveness Questionnaire (AG-87): aggressiveness	mean = 144.43 SD = 49.32	mean = 143.10 SD = 48.49	MD = −1.330; SD = 9.995		.027	56 (1 study)	42 (1 study)	⊕◯◯◯ Very low[a,c,d]	No significant effect ($P > .05$)
	Effect of typical versus atypical antipsychotics	Aggression. Aggressiveness Questionnaire (AG-87): physical manifest aggressiveness	mean = 26.46; SD = 10.9	mean = 25.38 SD = 10.05	MD = −1.080; SD = 2.153		.102	56 (1 study)	42 (1 study)	⊕◯◯◯ Very low[a,c,d]	No significant effect ($P > .05$)
	Effect of typical versus atypical antipsychotics	Aggression. Aggressiveness Questionnaire (AG-87): physical latent aggressiveness	Mean = 26.77; SD = 10.94	Mean = 26.55 SD = 11.13	MD = −0.220; SD = 0.9223		.02	56 (1 study)	42 (1 study)	⊕◯◯◯ Very low[a,c,d]	No significant effect ($P > .05$)
Stadtland[11]	Effect of olanzapine	Risk factors for aggressive behavior. Integrierte Liste der Risikovariablen (ILRV)	Mean = 8.35; SD = n/a	Mean = 5.96; SD = n/a	MD = 2.39; SE = n/a		.371	No	23 (1 study)	⊕◯◯◯ Very low[a,c,d,h,i]	Significant effect ($P < .001$)

Table 2. *Continued*

Publication	Intervention	Outcome	Control Condition (Treatment As Usual, TAU)	Intervention Condition	Absolute Effect	Relative Effect	Effect Size (Cohen's d)	Persons in Control Group (Studies)	Persons in Intervention Group (Studies)	Quality of the Evidence (GRADE)	Comments
Stadtland[10]	Effect of olanzapine	Aggressive behavior. Frequency of incidents: violence (general)			Decrease of violent incidents in 11 patients, increase in 1.		n/a	no	35 (1 study)	⊕◯◯◯ Very low[a,c,d,h,i]	
Stoner[23]	Difference between haloperidol and clozapine treatment	Aggressive behavior. Documented physically aggressive incidents leading to restraint or seclusion				OR = 0.333 [0.0900; 1.2351]	.606		Total: 84 (1 study)	⊕◯◯◯ Very low[a,b,c,d]	
Tavernor[24]	Effect of high- versus low-dose antipsychotics	Social Dysfunction and Aggression Scale (SDAS): general aggression	mean = 6.4; SD = 7		MD = 3.9; SE = 1.879		.525	32 (1 study)	32 (1 study)	⊕◯◯◯ Very low[a,c,d,j]	
	Effect of high- versus low-dose antipsychotics	Social Dysfunction and Aggression Scale (SDAS): peak aggression	mean = 12.2; SD = 10		MD = 5.8; SE = 2.395		.605	32 (1 study)	32 (1 study)	⊕◯◯◯ Very low[a,c,d,j]	

[a]Small sample size.
[b]No absolute description of outcome.
[c]No or insufficient allocation concealment.
[d]No or insufficient blinding.
[e]Offenses not clearly specified as violent incidents.
[f]Dosage restriction, no limitation.
[g]Aggression measured by necessity of PRN medication in case of agitation.
[h]Measure of risk factors rather than aggression/violence.
[i]Only 50% SSD patients.
[j]No data on intervention duration.

in-patients with schizophrenia and other severe mental disorders. The frequency and nature of violent incidents were recorded by treating clinicians and compared before and after olanzapine treatment started, using a study specific rating scale. The authors reported statistically significant reductions in four clinically relevant violence categories: "threatening behavior," "violence against fellow inpatients," "other aggressive acts," and "mild bodily harm." After correcting for multiple testing, only two measures, "threatening behavior" and "other aggressive acts," remained significant. The study did not use a control group and raters were not blind to treatment status, so again the quality of the study evidence must be considered very low.

Beck et al[19] investigated the impact of risperidone in patients with chronic treatment-resistant schizophrenia of three high-secure forensic psychiatry wards. The intervention group (n = 10) took oral risperidone up to 6 mg per day, while the control group (n = 10) received conventional antipsychotics and was matched to the intervention group for the level of clinical functioning using the Time-Sample Behavioral Checklist.[26] Violence was assessed via frequency counts of threatened and physical assaults as well as serious property destruction. Ratings were conducted twice: in the 6 months before and the 6 months after initiating treatment with risperidone in the intervention group, and before and after matching in the control group. The study reported a significant reduction in the frequency of all types of violent incidents in both groups pre and post treatment ($P < .0001$), but no significant difference between the risperidone group and the control group. Due to the lack of randomization and blinding, this study was considered of very low quality.

Gibbon et al[21] investigated the effectiveness of Risperidone long-acting injection (RLAI) across four UK high-secure forensic hospitals between 2004 and 2008, retrospectively investigating the clinical charts. In a subsample (n = 118) of their study, counts of violent and self-harm incidents were analyzed. About 25% experienced a lower number of incidents. There was once again neither randomization, nor control group.

In the course of an observational study, Brosseau et al[20] investigated the effect of omega-3 fatty acid supplements in forensic psychiatric inpatients with schizophrenia. Eicosapentaenoic acid and docosahexaenoic acid in either liquid or capsule forms were administered. Vitamin E was also added as an antioxidant. The frequency of incidents of agitated behavior were assessed via a count of the use of rescue pro re nata (PRN) medication. After 12 weeks of treatment, the mean number of PRN medication doses reduced from 32.7 to 22.6 ($P = .015$), and most symptom scores significantly reduced. Due to the indirect measurement of violence by PRN medication count, the small sample size (n = 12), the lack of blinding and randomization, this study has to be rated as very low quality.

Discussion

Violent behavior and its management in people with SSD is one of the core functions of forensic psychiatry. This literature review aimed to identify and present the best quality evidence for the use of pharmacological treatments in forensic settings for the management of violence in people with SSD. Although the search terms were formulated very broadly and multiple databases were searched, only 10 studies could be identified that met inclusion criteria. A recently published umbrella review[28] using "hard" criteria for violence such as police or hospital recorded violence or incarceration as well as the presence of a control group as inclusion criteria found no systematic review regarding medication or psychological interventions in forensic settings.

Type of antipsychotics

Three studies[18,23,25] investigated the effects of clozapine and all of them reported a reduction of violence. Unfortunately, none of these studies used a clear control group. Nevertheless, this finding is in agreement with studies among non-forensic psychiatric inpatients reporting a reduction of aggressive behavior among patients treated with clozapine.[14,29–32]

The effects of risperidone were studied in two studies. Gibbon et al[21] retrospectively investigating the clinical charts of 118 patients for the effects of RLAI and found that 25% experienced a reduction in violent incidents, but this study did not use a control group. Beck et al[19] investigated the effects of oral risperidone in only 10 patients compared to a matched control group. While the number of violent acts decreased during treatment with risperidone, this was not significant compared to the control group. It is possible that the different study designs, with and without control groups and different sample sizes, may account for the different results.

Stadtland and colleagues10, 11 reported from two studies that olanzapine use was associated with reduced violence. Both studies lacked a control group prohibiting any inferences about whether olanzapine was more effective than other psychotropic drugs.

Ruzic et al[22] compared forensic patients treated with SGAs and FGAs, but they found no differences in violent outcome. This finding is in contrast to studies in non-forensic settings which found that SGAs are superior to FGAs at reducing violence.[15,31]

Beside the studies focusing on SGAs, a study comparing daily doses of antipsychotic medications found that patients on higher doses were more violent.[24] The study design however probably tells us more about prescribing patterns than the effects of higher doses of antipsychotic medications. The effects of omega-3 fatty acid supplements on violence are very innovative,[20] but it was unclear how patients were assigned to the intervention.

Paucity of studies on pharmacological prescriptions in forensic settings

The most striking initial finding was the very small number of studies conducted in forensic psychiatry settings. We were surprised that we could identify only 10 studies. Half of them were observational and three were pre-post comparisons without control groups precluding any real conclusions about whether the drug under investigation had advantages compared to others. One study used a matched control design[19] and another was a non-randomized trial.[20] These two studies used very small samples (20 and 12 persons, respectively). In none of the papers we could find any information about power analyses used to estimate the initial sample size. Thus, it may be that many of the studies could have been simply too small and too badly designed to identify significant differences.

Despite the fact that we focused on SSD, sometimes small numbers of other subjects were included.[11] Most studies did not use research instruments such as the SCID to verify diagnoses. This also limits the applicability of any reported findings. Since psychiatric comorbidity, especially substance abuse and personality disorders, increase the risk for violence,[2,33] it is essential to know if the studies reported here excluded or included patients with such co-morbid diagnoses. Unfortunately, most authors did not consider psychiatric comorbidity which might affect the findings reported.

Assessment measures of violent behavior

Across the studies there was a variety of definitions and outcome measures used to identify and quantify the level of violence. Some studies used standardized and validated questionnaires, but two of them used outcomes which did not separate self-harm from violence against others.[21,24] It must be considered that this measurement uncertainty decreases the information yielded regarding violent behavior against other people. Several studies used non-standardized assessment methods, some of them locally developed questionnaires which prohibits comparisons with other studies. One study counted the number of rescue/PRN-medication administrations as indicators for violence, but PRN-medication can be used of course for other reasons also. The number of violence acts against staff or other patients or of the days in restraints can be influenced by a variety of local or national considerations, but are considered as clinically relevant by some authors.[28] In order to improve the comparability between studies, clear definitions, and standards are necessary.

Study designs

Beside the fact that we found only a small number of studies, we were nevertheless very surprised that we did not find a single RCT. RCTs are traditionally the gold standard for judging the benefits of treatments, as they allow us to attribute the observed effects to the treatments being compared.[34] Some authors[35,36] have discussed the advantages and limitations of RCTs compared to observational studies. Of course, all studies have some flaws in their design though it is still accepted that "The best RCT still trumps the best observational study".[34] Nevertheless, if there is no RCT to answer a specific question, then evidence from other study designs can be used.[34,36]

Leucht et al[37] in their very comprehensive meta-analysis reported from five RCTs that antipsychotics can clearly reduce violent or aggressive behavior. Thus, considering the fact that pharmacological treatments are the mainstream of treatment for SSD in general and certainly for SSD in forensic settings, the small numbers and the often low quality of the studies reported here is astonishing. One aspect hindering pharmacological research in mentally ill offenders in prisons and patients in hospitals are ethical and legal considerations. The Declaration of Helsinki[38] and the legal and ethical frameworks in many western countries greatly limit the extent to which pharmacological research can be conducted on people who are involuntarily detained, even if, in principle, informed consent to participate in the research project can still be given by the potential subjects. The fear is that people feel pressurized to participate in projects that perhaps they would not agree to, were they not involuntarily detained. It is argued that the goal of these legal restrictions is to protect these people from any risk of becoming subject to procedures that could potentially be harmful to them and that they would not otherwise agree to.

The cost of that position, however, is that currently people are detained against their wishes in hospital and often forcibly treated against their wishes with psychotropic drugs that often lack high-quality evidence establishing their effectiveness and side-effect profiles. This fact also raises ethical concerns. Beyond these ethical and research governance considerations, there are the practical challenges of conducting RCTs in psychiatric settings where the risk of violence to staff and other patients is real and may be immediate. However similar challenges have been overcome in psychiatric intensive care settings. It thus seems an imperative that we develop a framework for trials in forensic settings to allow us to get the evidence to support the best treatment with the lowest side-effects, in order to treat our patients effectively and in the least restrictive way.

Conclusions

Overall, because of the lack of good quality data and the methodological limitations of the studies that are available so far, it is not possible to draw any firm conclusions about the effectiveness of psychotropic medicines to reduce the risk of violence in patients with SSD in forensic settings specifically. There are challenges to conducting RCTs in forensic psychiatric settings, that include the ethical considerations described above. Large observational studies to identify current prescribing habits might be a next step to better understand current clinical practice. Such studies should use standardized diagnostic procedures for SSD and the associated comorbidities, use clear definitions of violence which can easily be compared with other studies and are clinically relevant (eg, number of violent attacks against other people in the hospitals, criminal violence, or incarceration). The use of standardized and validated assessment instruments for current and past clinical variables can improve the description of forensic samples. In addition, it is essential that future studies include samples that are sufficiently powered to confidently address the research questions that they attempt to address. Such studies may serve as feeders for future RCTs in order to understand which medicines are the safest and most effective to manage the risk of violence and improve forensic outcomes.

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Appendix: Search Terms Used for Electronic Data Bases

OVID—MEDLINE: 2,267
(exp “aggression”/ OR exp “self-injurious behavior”/ OR (exp “violence”/ NOT (exp “domestic violence”/ OR exp “gender-based violence”/ OR exp “intimate partner violence”/ OR exp “terrorism”/)) OR (“violen*” OR “*aggressi*” OR “agitat*” OR “assault*” OR “homicid*” OR (“*self” ADJ2 (“harm*” OR “injur*” OR “mutilat*” OR “destruct*”) OR “*suicid*”)).mp) AND (exp “schizophrenia spectrum and other psychotic disorders”/ OR (“severe” ADJ3 (“mental” OR “psychiatric”) ADJ3 (“disorder*” OR “illness*” OR “condition*” OR “disease*” OR “diagnos*”)).mp OR (“psychosis” OR “psychot*” OR “schizophreni*”).mp) AND ((exp “prisons”/ NOT exp “concentration camps”/) OR (exp “forensic psychiatry”/ NOT (exp “confidentiality”/ OR exp “insanity defense”/)) OR (exp “prisoners”/ NOT exp “prisoners of war”/) OR (“forensi*” OR “*prison*” OR “incarcerat*” OR “jail*” OR “peniten*” OR “convict*” OR “inmate*” OR “detention*” OR “arrest*” OR “detain*”).mp)
Filter: ≥ 1990
OVID—PsycINFO: 1501 / PSYNDEXplus: 312
(exp “aggressive behavior”/ OR exp “self-destructive behavior”/ OR (exp “violence”/ NOT (exp “domestic violence”/ OR exp “school violence”/ OR exp “intimate partner violence”/)) OR (“violen*” OR “*aggressi*” OR “agitat*” OR “assault*” OR “homicid*” OR (“*self” ADJ2 (“harm*” OR “injur*” OR “mutilat*” OR “destruct*”) OR “*suicid*”)).mp) AND (exp “psychosis”/ OR (“severe” ADJ3 (“mental” OR “psychiatric”) ADJ3 (“disorder*” OR “illness*” OR “condition*” OR “disease*” OR “diagnos*”)).mp OR (“psychosis” OR “psychot*” OR “schizophreni*”).mp) AND (exp “correctional institutions”/ OR exp “forensic psychiatry”/ OR exp “incarceration”/ OR (exp “prisoners”/ NOT exp “prisoners of war”/) OR (“forensi*” OR “*prison*” OR “incarcerat*” OR “jail*” OR “peniten*” OR “convict*” OR “inmate*” OR “detention*” OR “arrest*” OR “detain*”).mp)
Filter: ≥ 1990; “peer-reviewed journal”
SCOPUS: 2349
TITLE-ABS-KEY ((“violen*” OR “*aggressi*” OR “agitat*” OR “assault*” OR “homicid*” OR (“*self” W/2 (“harm*” OR “injur*” OR “mutilat*” OR “destruct*”) OR “*suicid*”)) AND ((“severe” W/3 (“mental” OR “psychiatric”) W/3 (“disorder*” OR “illness*” OR “condition*” OR “disease*” OR “diagnos*”)) OR (“psychosis” OR “psychot*” OR “schizophreni*”)) AND (“forensi*” OR “*prison*” OR “incarcerat*” OR “jail*” OR “peniten*” OR “convict*” OR “inmate*” OR “detention*” OR “arrest*” OR “detain*”)) AND PUBYEAR > 1989
Filter: “Article”
CINAHL—EBSCOhost: 287
(((MH “Aggression+”) NOT ((MH “Child Abuse”) OR (MH “Elder Abuse”) OR (MH “Stalking”) OR (MH “Student Abuse”) OR (MH “Verbal Abuse”) OR (MH “Community Violence”) OR (MH “Dating Violence”) OR (MH “Child Abuse, Sexual”) OR (MH “Munchausen Syndrome By Proxy”) OR (MH “Domestic Violence+”) OR (MH “Intimate Partner Violence”) OR (MH “Child to Parent Abuse”) OR (MH “School Violence”) OR (MH “Sibling Violence”))) OR (MH “Self-Injurious Behavior”) OR (MH “Suicide+”) OR (“violen*” OR “*aggressi*” OR “agitat*” OR “assault*” OR “homicid*” OR (“*self” N2 (“harm*” OR “injur*” OR “mutilat*” OR “destruct*”) OR “*suicid*”))) AND ((MH “Psychotic Disorders+”) OR (“severe” N3 (“mental” OR “psychiatric”) N3 (“disorder*” OR “illness*” OR “condition*” OR “disease*” OR “diagnos*”)) OR (“psychosis” OR “psychot*” OR “schizophreni*”)) AND ((MH “Prisoners”) OR (MH “Correctional Facilities”) OR ((MH “Forensic Psychiatry+”) NOT (MH “Insanity Defense”)) OR (“forensi*” OR “*prison*” OR “incarcerat*” OR “jail*” OR “peniten*” OR “convict*” OR “inmate*” OR “detention*” OR “arrest*” OR “detain*”))
Filter: “Wissenschaftliche Zeitschriften”(ie, Scientific journals)
Web Of Science (Core Collection) 1621
TS=((“violen*” OR “*aggressi*” OR “agitat*” OR “assault*” OR “homicid*” OR (“*self” NEAR/2 (“harm*” OR “injur*” OR “mutilat*” OR “destruct*”)) OR “*suicid*”) AND ((“severe” NEAR/3 (“mental” OR “psychiatric”) NEAR/3 (“disorder*” OR “illness*” OR “condition*” OR “disease*” OR “diagnos*”)) OR “psychosis” OR “psychot*” OR “schizophreni*”) AND (“forensi*” OR “*prison*” OR “incarcerat*” OR “jail*” OR “peniten*” OR “convict*” OR “inmate*” OR “detention*” OR “arrest*” OR “detain*”))
Filter: ≥ 1990; “Article”
EMBASE: 4825

No. Query	Results
#34 #19 AND #32 AND [1990-2018]/py	4,379
#33 #19 AND #32	4,944
#32 #22 OR #27 OR #30 OR #31	432 368
#31 forensi* OR prison* OR incarcerat* OR jail* OR peniten* OR convict* OR inmate* OR detention* OR arrest* OR detain*	432 368
#30 #28 NOT #29	15 189
#29 ‘prisoner of war’/de	471
#28 ‘prisoner’/exp	15 660
#27 #23 NOT #26	12 580
#26 #24 OR #25	28 350
#25 ‘insanity defense’:ti,kw	263
#24 ‘confidentiality’/de OR ‘professional secrecy’/de	28 087
#23 ‘forensic psychiatry’/de	12 996
#22 #20 NOT #21	14 536

Continued

#21 'concentration camp'/de	152
#20 'prison'/exp	14 688
#19 #13 AND #18	56 960
#18 #14 0R #15 0R #16 0R #17	510 165
#17 psychosis OR psychot* OR schizophreni*	478 221
#16 severe NEAR/3 (mental OR psychiatric) NEAR/3 (disorder* OR illness* OR condition* OR disease* OR diagnos*)	9,516
#15 'psychosis'/exp	278 320
#14 'schizophrenia spectrum disorder'/exp	181 063
#13 #1 OR #2 OR #9 OR #10 OR #11 OR #12	571 697
#12 suicid*	120 109
#11 self NEAR/2 (harm* OR injur* OR mutilat* OR destruct*)	16 812
#10 violen* OR aggressi* OR agitat* OR assault* OR homicid*	416 518
#9 #3 NOT #8	76 809
#8 #4 OR #5 OR #6 OR #7	62 355
#7 'terrorism'/exp	8,503
#6 'partner violence'/exp	9,899
#5 'gender based violence'/de	420
#4 'domestic violence'/exp	53 684
#3 'violence'/exp	131 650
#2 'automutilation'/de	15 780
#1 'aggression'/exp	95 095