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REVIEW

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A systematic review of the evidence of clozapine's anti-aggressive effects

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Abstract

Reducing the risk of violent and aggressive behaviour in patients with schizophrenia remains a clinical priority. There is emerging evidence to suggest that the second-generation antipsychotic, clozapine, is effective at reducing this risk in patients with schizophrenia and some evidence to suggest that it may be best in selected patients. We conducted a systematic literature search in March 2011 of all prospective and retrospective studies, which investigated clozapine's anti-aggressive effects in a variety of mental disorders. The review identified six animal studies, four randomized controlled trials, 12 prospective non-controlled studies and 22 retrospective studies, with four case studies. We found considerable evidence in support of clozapine's ability to reduce violent and aggressive behaviour. Clozapine's anti-aggressive effect was most commonly explored in patients with schizophrenia, with less evidence available for other psychiatric disorders, including borderline personality disorder, autistic spectrum disorders, post-traumatic stress disorder, bipolar disorder and learning disability. There was mixed evidence to address the question of whether or not clozapine was any more effective than other antipsychotics. In the case of schizophrenia, there was evidence to suggest that clozapine's anti-aggressive effect was more marked particularly in those with treatment-resistant illness. Its anti-aggressive effects appeared to be 'specific', being to some extent greater than both its more general antipsychotic and sedative effects. There were significant methodological inconsistencies in the studies we identified, particularly surrounding patient recruitment criteria, the definition and measurement of violence and the lack of randomized, controlled trials. Data on therapeutic monitoring were also limited. Clozapine can reduce violence and persistent aggression in patients with schizophrenia and other psychiatric disorders. It may offer an advantage over other antipsychotics, although perhaps exclusively in the case of traditionally defined 'treatment resistance' or more broadly defined 'complex cases' with co-morbidity. Larger, randomized, blinded, controlled studies with robust characterization of participants, and standardized measures of violence and aggression are, however, needed to fully understand this link and explore the possible mechanisms.

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Introduction

Schizophrenia and violence

Some patients with schizophrenia are at increased risk of being aggressive (Walsh *et al.* 2002). A recent systematic review and meta-analysis found that almost 10% of patients with schizophrenia or other psychotic disorders behaved violently, compared to less than 2% of the general public, with the risk of homicide up to 20 times higher (Fazel *et al.* 2009*a*). In the inpatient setting, aggression is even more common with rates of assault by patients with schizophrenia between 16% and 28% (Joyal *et al.* 2008; Krüger & Rosema, 2010). It is clear that the link between schizophrenia and any complex behaviour, including violence, is multi-factorial, involving both direct and indirect effects. Relevant factors include the presence of

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psychotic symptoms (Douglas *et al.* 2009; Link *et al.* 1998; Swanson *et al.* 2006), substance misuse (Fazel *et al.* 2009*b*; Smith & Hucker, 1994; Volavka & Swanson, 2010) conduct disorder (Swanson *et al.* 2008*a*) and co-morbid personality pathology (Hodgins *et al.* 2008).

Schizophrenia's impact on society is significant. In financial terms, the cost to the UK for 2004/2005 was estimated at £6.7 billion, with around £2 billion spent on direct clinical care alone (Mangalore & Knapp, 2007). Violence and the risk of violence disrupt treatment, and worsen, or are associated with a worse prognosis (Shrivastava *et al.* 2010). Furthermore, this link reinforces stigmatization in wider society (Phelan & Link, 1998).

Both first-generation (FG) and second-generation (SG) antipsychotics are effective at alleviating the symptoms of schizophrenia (APA, 2004; NICE, 2010). However, up to 40% of patients will not respond favourably 'despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics' (NICE, 2010) and will meet criteria for 'treatment resistance' (Kane *et al.* 1996).

Clozapine

It remains unclear if clozapine offers any advantages over other antipsychotics in the early phase of schizophrenia and in non-treatment-resistant cases (Girgis *et al.* 2011), although it is the only antipsychotic with proven efficacy in treatment resistance. Initial studies suggested that it is more effective at alleviating both positive and negative psychotic symptoms (Agid *et al.* 2011; Breier *et al.* 1994; Kane *et al.* 1988; Lindstrom, 1994) and improves overall functioning (Meltzer *et al.* 1990; Rabinowitz *et al.* 1996) in treatment-resistant patients. Recent meta-analyses suggest that while clozapine may not offer such a marked advantage for psychotic symptoms compared to the other SG agents, it has a greater effect on overall functioning in treatment resistance (Asenjo *et al.* 2010). Two other meta-analyses found that overall symptoms improve, particularly for the most symptomatic patients (Chakos *et al.* 2001) and that this may be most marked for negative symptoms (Leucht *et al.* 2009*a*, *b*). Furthermore, while clozapine might not offer a significant advantage in terms of overall mortality or employability, those on clozapine improved more frequently, and were less likely to relapse (Essali *et al.* 2009). This effect was again most prominent in treatment-resistant cases. In this review our aim was to specifically assess the effectiveness of clozapine as an anti-aggressive agent.

Method

Search strategy and inclusion criteria

We searched electronic databases: Scopus, Web of Knowledge, Medline, EMBASE, the Cochrane Library and PsycINFO, using the search terms 'clozapine' (also 'Clozaril', 'Azaleptin', 'Leponex', 'Fazacio', 'Froidir', 'Denzapine', 'Zaponex', 'Klozapol' 'Clopine') linked using the Boolean operators AND and OR to violen*, aggress*, schizophren*, psychos* in March 2011. We also searched for other psychiatric disorders such as borderline or emotionally unstable personality disorder, bipolar disorder and post-traumatic stress disorder. References lists were manually searched and cross-referenced. We did not apply any language or publication date limits and we contacted relevant researchers for any unpublished data.

We also searched the following registers for current clinical trials:

- WHO International Clinical Trials Registry Platform;
- International Standard Randomized Controlled Trial Number Register (ISTRCTN);
- NIH ClinicalTrials.gov (International);
- Australian New Zealand Clinical Trials Registry;
- Medical Research Council (MRC) Current Clinical Trials Register;
- NIHR Health Technology Assessment Programme (HTA) (UK).

We included all prospective controlled, non-controlled, retrospective and single case studies in the review, as long as they specifically investigated clozapine's efficacy at reducing aggression or violence in mental disorders. The search was not limited to a specific mental illness, although schizophrenia was the most frequently studied. We did not apply a minimum study duration, and allowed data from in-patient and outpatient samples. When two or more manuscripts examined the same sample, the most relevant paper was included.

Data extraction

A research assistant (C.F.) retrieved the references from the search and examined each in turn. We identified a total of 1267 studies. Clearly unsuitable manuscripts were rejected for further review. The full texts of the remaining documents were retrieved and cross-referenced against the inclusion criteria and checked by a second reviewer (M.P.). Any disagreements were resolved through discussion. Fifty-two studies entered our final qualitative synthesis.

Results

Clozapine and aggression in schizophrenia

The majority of the studies that have investigated the effects of clozapine on violent behaviour in schizophrenia employed open-label or retrospective designs, with four randomized controlled studies. Four review articles included some consideration of clozapine's anti-aggressive effects in schizophrenia (Citrome & Volavka, 2000; Glazer & Dickson, 1998; Topiwala & Fazel, 2011; Volavka & Citrome, 2008).

Animal models

Clozapine produced a dose–response reduction in aggression, without impairing locomotion at low dose (up to 1.5 mg/kg) in individually housed male mice (Garmendia *et al.* 1992) and in doses of 2 and 5 mg/kg in socially isolated mice (Rewerski *et al.* 1979) (Table 1). In rats with neonatal ventral hippocampal lesions (an animal neurodevelopmental model for schizophrenia) and high levels of aggression, acute clozapine (1 mg/kg) increased non-aggressive behaviour more than haloperidol (Becker & Grecksch, 2003); however, at higher dose and with longer exposure (5 mg/kg for 10 d) this effect was reversed, although clozapine still increased social interactions.

Acute clozapine (1 mg/kg) increased the latency to attack and reduced impulsivity to a novel intruder in 'early response gene' aggressive mice (Gallitano-Mendel *et al.* 2008) while longer dosing schedules (3.5 mg/kg.d for the first week, then 7 mg/kg.d for the second week) reduced aggressive and defensive behaviour and drove a reinstatement of investigative and sexual behaviour (Dixon *et al.* 1994), greater than any sedating effect, although these effects were inconsistent (Koike *et al.* 2009; McMillen *et al.* 1989).

Randomized controlled trials (*RCTs*)

Four RCTs found evidence that clozapine is more effective than comparators at reducing aggression in schizophrenia (Table 2). Niskanen *et al.* (1974) reported improvements in tension, hostility and excitement rated on the Brief Psychiatric Rating Scale (BPRS) compared to chlorpromazine in a double-blind design in patients with chronic schizophrenia, although with no differences on any other items. Subsequently, a small unblinded 14-wk study (Chow *et al.* 1996) randomized 15 aggressive inpatients with schizophrenia, schizoaffective disorder or dementia and psychosis either to clozapine or to remaining on their current antipsychotics. Clozapine improved aggression rated at 10 wk and 14 wk compared to baseline scores (Modified Overt Aggression Scale; MOAS), but with no significant differences in symptom scores (Positive and Negative Symptom Scale; PANSS).

Citrome *et al.* (2001) and Volavka *et al.* (2004) reported on a large 14-wk randomized double-blind study of 157 in-patients with chronic schizophrenia or schizoaffective disorder and sub-optimal treatment response, but otherwise not selected for high levels of aggression. Randomization was to clozapine, olanzapine, risperidone, or haloperidol. Clozapine was the only agent to reduce hostility on the PANSS, although the effect size was small (0.25). This was again independent of general antipsychotic effects and sedation. Furthermore, clozapine was more effective than haloperidol at reducing the number and severity of aggressive acts measured on the Overt Aggression Scale (OAS) and Total Aggression Severity (TAS), once an adequate clozapine dose had been achieved (mean 465.2 mg/d).

Finally, Krakowski *et al.* (2006, 2008) randomized 110 patients with DSM-IV schizophrenia or schizoaffective disorder, double-blinded to clozapine, olanzapine or haloperidol with follow-up for 12 wk. In this case, the participants were selected on the basis of a past history of aggression but did not have to meet traditional criteria for treatment resistance. Clozapine was associated with the lowest physical and verbal aggression scores (MOAS), and was better than haloperidol, but not olanzapine, at reducing violence against property. The three did not differ in their antipsychotic or sedative effects, while olanzapine had a better outcome in terms of cognition.

Crossover trials

Clozapine was more effective at reducing hostility and aggressive behaviour in patients with schizophrenia compared to placebo (Singer & Lam, 1973) and haloperidol, which was itself associated with an increase in aggression (Herrera *et al.* 1988), an effect reversed with clozapine and chlorpromazine (Table 3).

Prospective comparative studies against other medication

Five prospective, non-randomized, open-label studies compared clozapine's anti-aggressive properties to FG and SG antipsychotics (Table 4). Two found either no difference between the SG agents (Strous *et al.* 2006) or that olanzapine and risperidone were more effective at reducing aggression (Bitter *et al.* 2005), although neither included chronically ill or treatment-resistant patients.

Menditto *et al.* (1996) compared groups of patients with schizophrenia who either continued treatment as

Table 1. Summary of evidence for animal studies

Author	Design	Participants	Treatment	Outcome measure	Results
Koike *et al.* (2009)	RCT, double-blind	Socially isolated mice (aggressive) *vs.* group-housed mice (non-aggressive)	Clozapine, methylphenidate or fluoxetine	Social behavioural changes, social interaction test and novel object recognition test	Clozapine reduced aggression and completely inhibited biting and tail rattling but also reduced locomotion. Fluoxetine also reduced aggression
Gallitano-Mendel *et al.* (2008)	RCT, double-blind	Impulsive and aggressive mice with early response gene 3 *vs.* controls	Clozapine *vs.* placebo	Resident-intruder test of aggression	Low-dose clozapine reduced impulsiveness but not total aggression in ERG mice. Chronic dose reduced total aggression, but not as a result of sedation
Becker & Grecksch (2003)	RCT, double-blind	Lesioned rats (aggressive) *vs.* control	Clozapine *vs.* control, haloperidol *vs.* control, diazepam *vs.* control	Social interaction test	Acute clozapine increased non-aggressive behaviour in aggressive rats. Chronic clozapine treatment normalised time spent in social contact for aggressive rats but no effect on non-aggressive behaviour
Dixon *et al.* (1994)	Matched-pairs, controlled	Socially isolated mice (aggressive) *vs.* group-housed mice (non-aggressive)	Clozapine	Intruder mice paradigm	Clozapine reduced defensive behaviour and reinstated investigative and sexual activities in intruder mice
Gardmendia *et al.* (1992)	RCT, double-blind	Individually housed male mice (aggressive) *vs.* control	Clozapine: acute *vs.* chronic dosing	Standard opponents' 30 min after the last drug administration	Acute clozapine administration decreased 'attack' and 'threat' behaviours without impairing locomotion. Chronic clozapine treatment had no significant change on aggression
McMillen *et al.* (1989)	RCT, double-blind	Isolated aggressive mice *vs.* Controls	Clozapine, haloperidol, trifluoperazine, chlorpromazine, sulpiride, buspirone-HCl, rimcazole	Intruder mice paradigm	Clozapine very disruptive of motor activity; reduction in aggression was attributed to sedative effects
Rewerski *et al.* (1979)	RCT, double-blind	Socially isolated mice (aggressive)	Spiroperidol, pimozide and clozapine	Aggressive behaviours	Spiroperidol superior effect on aggression. Primozide and closapine had weaker, but significant anti-aggressive effect

RCT, Randomized controlled trial; ERG, early response gene.

Table 2. Summary of evidence for randomized controlled trial studies

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
Krakowski & Czobar (2011)	RCT, double-blind	Physically aggressive inpatients with DSM-IV schizophrenia or schizoaffective disorder	99	Clozapine, olanzapine or haloperidol	12 wk	MOAS, Executive function, PANSS, ESRS	Clozapine significantly reduced aggression. Baseline executive function predicted later aggression
Krakowski *et al.* (2008)			100			MOAS, PANSS and neurocognitive measures	Clozapine most effective in reducing aggression
Krakowski *et al.* (2006)			110			MOAS	Clozapine was superior to olanzapine and haloperidol in reducing total physical and verbal aggression
Volavka *et al.* (2004)	RCT, double-blind	Inpatients with chronic schizophrenia or schizoaffective disorder with PANSS > 60. Sub-optimal treatment response to 1+ FGA. 85% male.	157	Clozapine, olanzapine, risperidone or haloperidol	14 wk	OAS	Clozapine was superior to haloperidol reducing aggression
Citrome *et al.* (2001)						Hostility item on PANSS	Clozapine was the only drug to significantly reduce hostility scores
Chow *et al.* (1996)	RCT	Inpatients with DSM-III-R psychosis (12 schizophrenia, 2 schizoaffective disorder, 1 dementia with psychosis)	15	Clozapine or other antipsychotic	14 wk	PANSS, MOAS	MOAS scores of the clozapine group were improved at a weeks 10 & 14 compared to baseline. PANSS did not improve for either group
Niskanen *et al.* (1974)	RCT, double-blind	Patients with schizophrenia, 27 male, 21 female. 75% acute or exacerbation of chronic schizophrenia	48	Clozapine or chlorpromazine	40 d treatment	BPRS, somatic examinations	Psychomotor symptoms tension, aggression and excitement, improved in clozapine-treated group compared to baseline. No differences in psychotic symptoms

RCT, Randomized controlled trial; MOAS, Modified Overt Aggression Scale; PANSS, Positive and Negative Symptom Scale; ESRS, Extrapyramidal Side-effect Rating Scale; FGA, first-generation antipsychotic; OAS, Overt Aggression Scale; BPRS, Brief Psychiatric Rating Scale.

Table 3. Summary of evidence for crossover studies

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
Herrera *et al.* (1988)	Crossover study	Male patients diagnosed with TR schizophrenia (DSM-III). Did not have unusual histories of violence	16	Haloperidol, followed by either clozapine or chlorpromazine	2 wk placebo, 6 wk haloperidol, 2 wk placebo, 6 wk clozapine or chlorpromazine	BPRS, SAREE, Lions Scale of Inpatient Violence	Significantly more aggression in haloperidol than placebo or clozapine/chlorpromazine period
Singer & Lam (1973)	Double-blind, crossover	Inpatients diagnosed with schizophrenia Mean age = 34.4 yr, 22 were male	30	Clozapine and placebo	4 wk clozapine, 2 weeks placebo, 4 wk clozapine	CGS, BPRS	BPRS and CGS improved particularly: anxiety, tension, hostility, excitement. Both clozapine and placebo improved hallucinations, grandiosity and unusual thought content

TR, Treatment resistant; BPRS, Brief Psychiatric Rating Scale; SAREE, Simpson–Angus Rating Scale for Extrapyramidal Effects; CGS, Clinical Global Scale.

usual or switched to clozapine, although they did not indicate whether study protocol or suboptimal clinical response motivated these changes. Violent acts declined following the switch to clozapine compared to those who continued with their regular treatment, while the clozapine group also did better in terms of use of their rehabilitation programme.

In the longest study (a 2-yr observational study), Swanson *et al.* (2004), found that SG antipsychotics, clozapine, risperidone and olanzapine all decreased the risk of violence (MacArthur Community Interview) compared to FG agents or those who remained antipsychotic free. Over a 6-month period, Spivak *et al.* (2003) found that oral clozapine was more effective than haloperidol-decanoate depot for aggression (OAS), suicidality (OAS, HAMD), impulsiveness (Impulsivity Scale) and low mood (HAMD) in outpatients with schizophrenia. Only those allocated clozapine met criteria for treatment resistance while none of the patients were specifically selected for either their baseline aggressive or suicidal behaviour. Impulsivity, aggression and suicidality did not differ between the clozapine 'responders' and 'non-responders', which was interpreted as evidence that clozapine's anti-aggressive effects were independent of its antipsychotic effects.

Prospective within-subject pre- vs. *post-clozapine studies*

Several prospective pre- *vs.* post-clozapine trials have produced promising results in schizophrenia (Table 5). Clozapine reduced the number of violent incidents (Ebrahim *et al.* 1994; Wilson, 1992) and the frequency of seclusion and restraint (Chiles *et al.* 1994) in inpatients with treatment-resistant schizophrenia in US state and high-security hospitals (Ebrahim *et al.* 1994). Furthermore, in treatment-resistant aggressive patients with schizophrenia, clozapine reduced the number of incidents, time in seclusion and restraint, the use of rapid tranquillization and symptom (BPRS) scores (De Domenico *et al.* 1999). Three other studies (Buckley *et al.* 1995; Spivak *et al.* 1997; Volavka *et al.* 1993) found that clozapine reduced aggression and impulsivity in treatment-resistant patients with schizophrenia in a manner distinct from symptomatic improvement.

Retrospective studies

Twenty-two retrospective studies and four single case studies, mostly in inpatient settings have explored clozapine's effect on aggression in schizophrenia retrospectively (Table 6). All reported some degree of improvement with clozapine compared to the

Table 4. Summary of evidence for prospective studies comparing clozapine to other medication

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
Strous *et al.* (2006)	Prospective, open-label, non-randomized	Inpatients and outpatients with chronic schizophrenia or schizoaffective disorder (DSM-IV)	131	Clozapine, risperidone or olanzapine	12 wk	PANSS, HAMD, HAMA, OAS, IS, CGI and adverse effects	No differences in depression, anxiety, EPS or aggression
Bitter *et al.* (2005)	Prospective, open-label, non-randomized	Inpatients and outpatients with schizophrenia (DSM IV or ICD 10); 27 developing countries	3135	Clozapine, quetiapine, olanzapine, risperidone, haloperidol (clinicians choice)	6 months	Clinician report	Olanzapine and risperidone superior to clozapine and haloperidol
Swanson *et al.* (2004)	Prospective, observational, open-label, non-randomized	Patients with schizophrenia spectrum disorders (DSM-IV). 21% co-morbid substance abuse. 15.3% previous violence	229	Clozapine, risperidone, olanzapine, conventional neuroleptics, none	2 yr	MacArthur Community Violence Interview, record review	Risk of violence reduced in second generation compared to first generation
Spivak *et al.* (2003)	Prospective, open-label, non-randomized	Patients with chronic schizophrenia (DSM-IV). PANSS >70. All 18 on clozapine were considered TR	44	Clozapine or haloperidol-depot	6-month trial	PANSS, HAMD, OAS, IS	Reductions on all outcomes higher in clozapine
Menditto *et al.* (1996)	Prospective, open-label, non-randomized	Inpatients with chronic schizophrenia (DSM-III-R). Many high rates of previous aggression	22	Clozapine or traditional medication	6 months	TSBC, Aggressive behaviour frequency counts	Clozapine improved response to behavioural programme and significant decrease in aggression

PANSS, Positive and Negative Symptom Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; OAS, Overt Aggression Scale; IS, Impulsivity Scale; CGI, Clinical Global Impression Scale; EPS, Extrapyramidal Symptoms; TR, treatment resistant; TSBC, Time-Sample Behavioural Checklist.

Table 5. Summary of evidence for prospective studies comparing pre *vs.* post clozapine within-subjects

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
De Domenico *et al.* (1999)	Prospective/ retrospective, non-randomized, open-label	Aggressive inpatients with TR schizophrenia (DSM-IV) and mental retardation	16	Clozapine	24 months	ASDS, seclusion and restraint data, no. of chemical interventions, BPRS	Clozapine reduced number of aggressive acts, time spent in seclusion and restraint, emergency medication and BPRS scores
Spivak *et al.* (1997)	Prospective, open-label, non-randomized	Inpatients with chronic TR schizophrenia (DSM-IV)	14	Clozapine or traditional antipsychotic	18 wk	PANSS, OAS, IS	Clozapine decreased impulsiveness (32%) and aggressiveness (98%)
Buckley *et al.* (1995)	Prospective, open-label, non-randomized	Patients with TR schizophrenia (DSM-III-R), 11 considered violent	30	Clozapine	12 months	BPRS, seclusion and restraint records	Significant reductions in time spent in seclusion and restraint with clozapine
Chiles *et al.* (1994)	Prospective, open-label, non-randomized	Inpatients with TR schizophrenia or schizoaffective disorder 22 with axis II personality disorder	115	Clozapine	Up to 26 wk	Seclusion and restraint rate incidents & some data from NOISE ($n=84$)	Clozapine treatment significantly reduced seclusion and restraint
Ebrahim *et al.* (1994)	Prospective, open-label, non-randomized	Forensic inpatients with TR schizophrenia (mainly paranoid) or schizoaffective disorder (DSM-III-R) All male & aggressive	27	Clozapine	6 months	Review of medical records (BPRS, levels of privileges)	Zero restraint after six months on clozapine. 70% achieved increased privileges
Volavka *et al.* (1993)	Prospective, open-label, non-randomized	Inpatients with TR schizophrenia (DSM III-R) across 21 US State Hospitals All patients poor functioning for 5 years	223	Clozapine	Up to 1 yr	Hostility score was compared to psychosis score on BPRS	Clozapine produced significant improvement on hostility item over time
Wilson (1992)	Prospective and retrospective, open-label, non-randomized	Chronic TR schizophrenia (DSM IV). Preference given to more symptomatic patients	37	Clozapine	12 months	BPRS, AIMS, records review	Patients improved on clozapine

TR, Treatment resistant; ASDS, Aggression and Social Dysfunction Scale; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale; OAS, Overt Aggression Scale; IS, Impulsivity Scale; NOISE, Nurses Observation Scale for Inpatient Evaluation; AIMS, Abnormal Involuntary Movement Scale.

Table 6. Summary of evidence for retrospective studies

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
Balbuena *et al.* (2010)	Retrospective, case note review	Psychiatric inmate with psychoses (DSM-IV) or related disorders	98	Clozapine or other antipsychotics	6 months	Chart review	Patients on other APs greater improvement (BPRS) but higher number of incidents. Clozapine more likely to increase pay
Beer *et al.* (2007)	Retrospective	Inpatients with schizophrenia, schizoaffective or affective disorder	31	Clozapine	7 yr	Case note review	Incidents per month reduced by over 75%
Kranzler *et al.* (2005)	Retrospective	Aggressive patients with TR schizophrenia or schizoaffective disorder	20	Clozapine	6 months	Chart review	Clozapine decreased frequency emergency medication and seclusion
Smith & White (2004)	Retrospective, Cross-sectional	Outpatients with schizophrenia or schizoaffective disorder at a forensic day hospital	32	Clozapine or non-clozapine	One point in time	SBS	10% clozapine patients severe score on the SBS hostility scale *vs.* 62% non-clozapine
Stoner *et al.* (2002)	Retrospective, case note review	Forensic patients hospitalized in the US with substance abuse and schizophrenia	84	Clozapine or haloperidol	1 January 1990 to 1 August 1999	GAF, Chart review	Clozapine patients more likely to obtain conditional release and stayed out for longer
Chengappa *et al.* (2002)	Retrospective	Inpatients with schizophrenia or schizoaffective disorder.	137	Clozapine	Up to 12 months before and after	Seclusion and restraint	Clozapine reduced seclusion and restraint *vs.* pre-clozapine
Chalasani *et al.* (2001)	Retrospective, case note review	Adolescent inpatients with severe childhood-onset schizophrenia and persistent psychotic symptoms	6	Clozapine	Long-term	Chart review	Clozapine improved social interactions and decreased violent and suicidal behaviours. GAF improved significantly
Frankle *et al.* (2001)	Retrospective	Outpatients with DSM-IV psychotic diagnosis with criminal histories	165	Clozapine or non-clozapine	One point in time	Chart review, arrest rate	Clozapine associated with reduction arrest rate, greater than gender, education, onset of illness or recency of birth
Sharif *et al.* (2000)	Retrospective	Patients with a diagnosis of schizophrenia (DSM-IV)	24	Clozapine or risperidone	At least 6 wk	Chart review	Clozapine response rate 38% positive symptoms, 29% negative symptoms, 71% aggressive behaviour *vs.* risperidone (17%, 8%, 41% respectively)

Table 6 (*cont.*)

Author	Design	Participants	No.	Treatment	Duration	Outcome measure	Results
Swinton & Haddock (2000)	Retrospective, case note review	Inpatients (high security hospital) and matched-controls for age and year of admission and gender	212	Clozapine	Up to 7 yr	Rates of discharge	At 2 years, 25% on clozapine discharged *vs.* 10% controls At 4 years, 50% on clozapine discharged *vs.* 25% controls
Volavka (1999)	Retrospective analysis of NYOMH database	Inpatients with TR schizophrenia (DSM-III-R)	331	Clozapine	Approximately 47 wk	BPRS	Overt aggression reduced to 1% compared to 31% previously
Dalal *et al.* (1999)	Retrospective, naturalistic analysis	Inpatients in a hig- security hospital with schizophrenia	50	Clozapine	2 yr follow up	Chart review	52% reduction in severity of positive symptoms and 80% subgroup (previous aggression) decrease in violent behaviour after 1 year. 19/50 discharged within 4 yr
Spivak *et al.* (1998)	Retrospective	TR schizophrenia. All patients had similar levels of aggression	60	Clozapine or classic antipsychotic	1 yr	PANSS, HAMD, HAMA, OAS, IS.	Lower levels of aggression, sucidality and impulsiveness in clozapine compared to FGA Two groups similar on PANSS
Gelly *et al.* (1997)	Retrospective/ clinical experience	TR schizophrenia (ICD 10), some with mental retardation and childhood disintegrative disorder	20	Clozapine	Range: 3 months to 7 yr	Chart review. BPRS, GAF and CGI	Clozapine alleviated severe behaviour problems
Boachie & McGinnity (1997)	Retrospective	15/17 patients TR schizophrenia Others had mild/moderate disability	17	Clozapine	Case notes from January 1991 and December 1994	Chart review	Improvement marked in 47% and substantial in 76%. Reduction in aggression an important indicator of improvement
Rabinowitz *et al.* (1996)	Retrospective review	Inpatients with schizophrenia (DSM-IV)	75	Clozapine	3–9 months before and 6 months after	Chart review	49% less physical aggression, 70% fewer verbal aggression and significant decreases in BPRS hostility, PANSS, and psychosis
Wilson & Claussen (1995)	Retrospective	TR schizophrenia, schizoaffective disorder, bipolar affective disorder or organic delusional disorder	100	Clozapine	6 months before and 18 months of treatment	Chart review	Violent episodes in hospital decreased in first 6 months. 45 patients much improved, and 18 somewhat improved

Rimon *et al.* (1994)	Retrospective	Inpatients with TR schizophrenia (DSM-III-R)	103	Clozapine	12 months before and 12 months after	Chart review	Significant decrease anxiety and aggression after 3 months. 12 months: 37% patients discharged and 70% clearly benefited
Reid *et al.* (1994)	Retrospective	Inpatients with chronic schizophrenia (DSM-III-R)	172	Clozapine	Up to 2.5 yr	Bed days	Bed-days reduced by average of 132 days per year at 1.5 years, 166 days per year at two years, and 201 days per year at 2.5 yr
Ratey *et al.* (1993)	Retrospective chart review	Psychotic inpatients on specialized unit for the severely aggressive	5	Clozapine	12 months	Chart review	Clozapine reduced all aggression outcomes, despite little affect on psychotic symptoms
Maier *et al.* (1992)	Retrospective	TR schizophrenia or schizoaffective disorder and forensic status	25	Clozapine	6 months	Chart review	13 improved (release granted or advanced to lower security)
Mallyer *et al.* (1992)	Retrospective	Patients receiving clozapine in a state mental hospital	107	Clozapine	13 months	Restraint and seclusion records	Frequency and time in seclusion and restraint decreased with clozapine
Milovanovic *et al.* (1974)	Retrospective/ clinical experience	Various schizophrenia spectrum disorders	137	Clozapine	2 yr experience	Medical records	Complete clinical remission 65%. Most in psychomotor agitation and aggression (75%), hallucinations (69%), delusions (65%), and anxiety (61%)

BPRS, Brief Psychiatric Rating Scale; APs, antipsychotics; TR, treatment-resistant; SBS, Social Behaviour Schedule; GAF, Global Assessment of Functioning Scale; IM, intramuscular; NYOMH, New York State Office of Mental Health; PANSS, Positive and Negative Symptom Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Rating Scale; OAS, Overt Aggression Scale; IS, Impulsivity Scale; FGA, first-generation antipsychotic; CGI, Clinical Global Impression Scale.

previous treatments which included FG and SG agents. The studies varied in their entry criteria and outcome measures and the follow-up time-frame. Fifteen of these retrospective studies focused on forensic inpatient samples (Balbuena *et al.* 2010; Beer *et al.* 2007; Boachie & McGinnity, 1997; Chengappa *et al.* 2002; Dalal *et al.* 1999; Maier, 1992; Mallyer *et al.* 1992; Rabinowitz *et al.* 1996; Ratey *et al.* 1993; Reid *et al.* 1994; Rimon *et al.* 1994; Sharif *et al.* 2000; Stoner *et al.* 2002; Swinton & Haddock, 2000; Wilson & Claussen, 1995), while two more looked at outpatients with criminal histories (Frankle *et al.* 2001; Smith & White, 2004). All agreed that clozapine had a beneficial effect on violence and aggression in these forensic settings.

Two retrospective studies in two of the UK's high-security hospitals (Ashworth, Rampton) found that clozapine reduced violent behaviour (Dalal *et al.* 1999) and speeded clinical progress (Swinton & Haddock, 2000). Both reported greater clinical improvement allowing transfer to either lower levels of security (Dalal *et al.* 1999) or to institutions with a larger number of people (Swinton & Haddock, 2000). Balbuena *et al.* (2010) found that patients with DSM-IV psychoses treated with clozapine were more likely to receive a pay increase, reflecting favourable functional performance over a period of 3–6 months. Furthermore, almost 60% of serious offenders (life imprisonment) treated with clozapine were offence-free at the end of a 6-month trial, compared to 25% of non-clozapine-treated serious offenders. Those on other antipsychotics experienced more favourable outcomes in terms of symptom scores (BPRS).

In outpatient mentally disordered offenders with psychosis, the best predictor of reduced arrest rate was clozapine (Frankle *et al.* 2001), while in a forensic day hospital setting, those on clozapine were less hostile and aggressive (Smith & White, 2004).

Clozapine reduced violence and aggression in a low-security challenging behaviour unit (Beer *et al.* 2007) and in a specialist unit for patients with severe aggressive behaviour (Ratey *et al.* 1993), despite little effect on psychotic symptoms. Volavka (1999) found a reduction in aggression for patients on clozapine across 21 hospitals, the effect again greater than any antipsychotic or sedative effect. Others (e.g. Rabinowitz *et al.* 1996) found incidents of physical and verbal aggression were reduced more than symptoms or an increase in sedation, in an Israeli public psychiatric hospital.

Seclusion and restraint fell by more than 90% and 80%, respectively, in inpatients in a state hospital following clozapine initiation (Mallyer *et al.* 1992) and in a large ($n = 137$) study within a US state psychiatric hospital (Chengappa *et al.* 2002). Others have found that violent incidents decreased (Wilson, 1992) as did bed days after 1.5 yr of clozapine treatment (Reid *et al.* 1994), the advantage increasing year on year with continued treatment, while there was again little or no effect on psychotic symptoms (Gelly *et al.* 1997). Stoner *et al.* (2002) found that those on clozapine were more likely to achieve a conditional release and to stay out of hospital on release for longer, while both aggression and anxiety were decreased with clozapine treatment in a central mental hospital in Finland (Rimon *et al.* 1994), with 37% being discharged at 12 months.

Children

Clozapine reduced the number of violent, homicidal and suicidal behaviours (Chalasani *et al.* 2001), in adolescents with early onset schizophrenia and significantly decreased the frequency of emergency sedation and seclusion in a state hospital (Kranzler *et al.* 2005).

Reviews of the pharmacological treatment of aggression in schizophrenia

Glazer & Dickson (1998) examined 11 studies available at the time that included data on clozapine's anti-aggressive properties in schizophrenia, although with no RCTs. Each study found beneficial effects for clozapine compared to a pre-clozapine phase and the authors' proposed five possible mechanisms for clozapine's apparent advantage, these included greater effects on:

(1) positive psychotic symptoms;
(2) negative psychotic symptoms;
(3) motor side-effects, such as akathisia;
(4) substance abuse;
(5) suicidality.

Two other reviews considered the broad pharmacological management of aggression and violence in schizophrenia (Topiwala & Fazel, 2011; Volavka & Citrome, 2008). Volavka & Citrome (2008) reported evidence of clozapine's 'anti-aggressive' effects but noted the poor evidence quality. They too concluded that clozapine's anti-aggressive effects went beyond its antipsychotic properties and might include reduced substance misuse and impulsivity, increased monitoring and surveillance compliance, increased treatment concordance, and a generally better outcome. More recently, Topiwala & Fazel (2011) were able to include eight randomized controlled therapeutic trials of antipsychotics. Clozapine was again noted to offer superior anti-aggressive effects, while there was little

to discriminate between the FG or SG antipsychotics, although the authors emphasized overall the overwhelming importance of ensuring treatment compliance.

Suicide

The conceptual, epidemiological and phenomenological links between aggression to others and aggression against the self are well recognized across a variety of mental disorders (Dyer *et al.* 2009; Hillbrand, 1995; Ilgen *et al.* 2010; Steinert *et al.* 1999), and clozapine's ability to reduce suicidal behaviour in some has been recognized. A meta-analysis reported a 3-fold reduction in suicidal behaviour in patients treated with clozapine compared to other treatments (Hennen & Baldessarini, 2005). However, many of the studies were methodologically poor and the single RCT found no effect on the 'completed suicide' rate (Meltzer *et al.* 2003). Nonetheless, there was a significant reduction in attempted suicides that needed hospitalization or other emergency interventions. Spivak *et al.* (1998) found fewer suicide attempts in treatment-resistant patients treated with clozapine, compared to FG antipsychotics, while Meltzer & Okayli (1995) reported an 88% decrease in the rate of suicide, and Modestin *et al.* (2005) found a 12-fold decrease in the risk of suicidal behaviour with clozapine.

A national 11-yr follow-up study in Finland (FIN11; Tiihonen *et al.* 2009) examined the causes of mortality in patients with schizophrenia under outpatient care on the basis of current and cumulative antipsychotic exposure. The lowest risk for both overall mortality and suicide was in those treated with clozapine. However, the study has been criticized (De Hert *et al.* 2010) for failing to report all the data, idiosyncratic drug selection and comparisons, failure to address confounders and exclusion of deaths during hospitalization, which accounted for 64% of all deaths.

Analysis of the Texas Clozapine Registry found only one suicide in 6 yr (Reid *et al.* 1998). Furthermore, Walker *et al.* (1997) reporting a study of the US Clozaril National Registry between April 1991 and December 1993, found a marked reduction in the incidence of suicide in those on clozapine, with the highest suicide rates found in those who had stopped clozapine. Munro *et al.* (1999) used the Clozapine Patient Monitoring Service (CPMS) data in the UK to examine data on almost 13 000 patients treated with clozapine between January 1990 and April 1997. The suicide rate in the cohort was 498 compared to a standardized mortality ratio of around 2000 in non-clozapine-treated patients with schizophrenia.

Others have, however, questioned clozapine's efficacy in reducing suicide. Modai *et al.* (2000) found the rate of suicide among patients currently receiving clozapine was 3.6 times higher than among non-clozapine-treated patients, although the limited number of deaths from all causes in this study should be noted. Sernyak *et al.* (2001) found inpatient veterans with schizophrenia who were treated with clozapine, were significantly less likely to die during follow-up compared to patients with schizophrenia on other medication, although there were no significant differences in the rates of completed suicide.

Clozapine and aggression in other non-psychotic disorders

Clozapine's anti-aggressive effects may not be restricted to schizophrenia. Clozapine effectively improves BPRS and Global Assessment Scale (GAS) scores in patients with emotionally unstable borderline personality disorder (BPD; Frankenburg, 1993), also reducing aggression against self, including physical mutilation (Chengappa *et al.* 1999; Swinton, 2001) and suicidal behaviours (Benedetti *et al.* 1998) in severe cases of BPD. Many of these patients may have experienced psychotic or quasi-psychotic symptoms; however, Parker (2002) has shown that clozapine reduces aggression whether directed at self or others in BPD patients, independently of changes in psychotic-type symptoms. The patients' aggression also rapidly re-occurred if clozapine was discontinued, and improved when reinstated.

Several small open-label studies suggest that clozapine exerts anti-aggressive effects in people with autistic spectrum disorders and aggression (Beherec *et al.* 2011; Gobbi, 2001; Zuddas *et al.* 1996), the effect greater than other antipsychotics (risperidone, haloperidol) (Lambrey *et al.* 2010). There is evidence that clozapine can reduce aggressive behaviour in patients with bipolar disorder (Kowatch *et al.* 1995) and post-traumatic stress disorder (Wheatley *et al.* 2004), although in both, the patients also experienced psychotic symptoms. Nonetheless, Kraus & Sheitman (2005) have reported reduced violent behaviour in a variety of diagnostic groups both with and without psychotic symptoms treated with clozapine. Furthermore, there are several small studies and case reports that suggest that clozapine leads to a significant reduction in aggressive behaviour in patients with learning disabilities (Cohen & Underwood, 1994; Hammock *et al.* 2001; Michals *et al.* 1993).

Discussion

The study data show that clozapine appears to offer an anti-aggressive effect in schizophrenia and psychosis, possibly greater than any other antipsychotic. This anti-aggressive effect is also seen in patients with other psychiatric disorders including emotionally unstable BPD, autistic spectrum disorders, post-traumatic stress disorder and learning disability, although the breadth and quality of data is even more circumspect. The majority of studies speculate, that at least some of clozapine's anti-aggressive advantages were 'specific', i.e. independent both of its more generic antipsychotic and sedative effects. These conclusions were based primarily on the statistical independence of the results and secondly on observations that the reductions in violence exceeded the relatively modest improvements in psychotic symptom control and were temporally distinct and longer lasting than changes in sedation.

The small number of animal studies produced mixed results but can still shed some light on the question of clozapine's anti-aggressive mechanism. There was some consistency to the observation, also seen in the human studies, that clozapine's anti-aggressive effects were independent of sedation, but not of locomotor activity. This raised the prospect that clozapine's effect may in part be mediated by an anxiolytic as opposed to an exclusively antipsychotic effect (Becker & Grecksch, 2003; Gallitano-Mendel *et al.* 2008). This coupled with the prominent position that the serotonergic system may play in the biology of impulsivity and aggression (Popova, 2008; Popova *et al.* 2010) ties in well with the hypothesis that it is clozapine's complex receptor-binding affinities for D_2 and D_4, but also 5-HT_{2A}, receptors that could underpin its anti-aggressive effects.

Notwithstanding these conclusions, there are a number of methodological weaknesses that limit our interpretation of many of these studies. First, the most robust way to establish clozapine's comparative effects on aggression is through randomized controlled clinical trials, at present there are only four within the literature. This paucity of data is likely, in part, to reflect the recruitment and retention challenges that result from the methodological rigours of a RCT, and that they are particularly difficult to implement in groups with mental illness and high rates of aggression. A second limitation relates to the study endpoints and the inconsistent definition of what violence represents. Across the studies reviewed, violence varies from a subjective symptom of tension or irritability to overt physical assault. There is no consensus across studies of where in particular the lower threshold of that concept lies (Topiwala & Fazel, 2011). One strategy to address this failure is to use structured data collection guides such as the OAS (Yudofsky *et al.* 1986) and MOAS (Kay *et al.* 1988) to both define and quantify more objectively violence data collection. It has been suggested that the scope of study endpoints should be broadened. Some have criticized studies for focusing exclusively only on violence as a therapeutic outcome and suggest that besides violence future studies should incorporate patient-centred functional outcomes, with an emphasis on recovery (Asenjo *et al.* 2010). This is timely, although it is difficult to conceive of patients progressing along a recovery-focused pathway, while still manifesting high levels of aggression and violence.

Patient selection strategies were inconsistent across the studies, and may lie at the heart of clozapine's advantage. It may be particularly important to define whether the patients are clinically 'complex' with comorbidities such as substance misuse, or poor treatment concordance, or are truly 'treatment resistant' in terms of a history of failing to respond to adequate previous antipsychotic treatment. Almost by definition long-stay inpatient and 'forensic' psychiatry samples tend to be a mixture of these two, and true treatment resistance can often be difficult to identify robustly.

The nature of the link between schizophrenia, psychotic symptoms and violence remains contentious. Only a minority of assaults (20%) committed by inpatients with psychosis are directly attributable to positive psychotic symptoms (Nolan *et al.* 2003), with other psychopathology and disordered impulse control implicated for the remainder. However, in those patients where psychosis is a driving factor, certain symptoms, for instance delusions of threat and control override (Link *et al.* 1998) or hostility, persecution, certain hallucinatory experiences, grandiosity and excitement are linked to an increased risk of violence (Swanson *et al.* 2006). In a recent meta-analysis Douglas *et al.* (2009), concluded that psychotic symptoms, in the context of a variety of psychiatric disorders with psychosis (for instance all schizophrenia spectrum disorders, or depression with psychotic symptoms), was reliably and significantly associated with a 49–68% increase in the odds of violence, although the effect size was small (0.24–0.32).

In terms of patient selection, it may be that clozapine's anti-violent effects are particularly prominent in those patients who are persistently aggressive (Krakowski *et al.* 2006), chronically ill (Menditto *et al.*

1996) or more formally 'treatment resistant' (Chiles *et al.* 1994). Some have suggested that clozapine is most effective in the subpopulation of treatment-resistant patients who have failed to respond to FG antipsychotics and continue to manifest persistent aggression (Buckley & Shendarkar, 2005; Buckley *et al.* 1995). While it should be noted that in the majority of prospective studies the patients met 'treatment-resistant' criteria, the four RCTs did not restrict themselves to that group, but rather to chronic patients. Furthermore, some studies reported in this review included patients that were not 'treatment resistant', yet still improved with clozapine.

While violence and aggression in schizophrenia are aetiologically heterogeneous, it is likely that clozapine exerts its anti-aggressive effects through a number of pathways (Volavka & Citrome, 2008). To date the evidence appears to suggest that clozapine's anti-aggressive effect is greater than its more general antipsychotic or sedative effects. Patients with schizophrenia manifest greater impulsivity and poor impulse control (Averbeck *et al.* 2011; Nolan *et al.* 2011). This deficit may underpin or compound the tendency to aggression in some patients (Barrett, 2011; Iancu *et al.* 2010; Kumari *et al.* 2009), particularly in the context of heightened anxiety (Lincoln *et al.* 2010). Trait impulsivity often represents a specific treatment target for aggression, although evidence supporting, for instance, the use of anticonvulsants in this context is very limited (Huband *et al.* 2010). It may be that clozapine reduces *impulsivity* in schizophrenia (Dursun *et al.* 2000; Spivak *et al.* 1997; Strous *et al.* 2006) more than other antipsychotics and for instance also in emotionally unstable BPD type (Benedetti *et al.* 1998). However, none of these studies reviewed or adequately established baseline impulsivity scores. Notably, Spivak *et al.* (1998) reported that improvements in aggression were both faster and more prominant than reductions in impulsivity, suggesting that the two may not be so closely linked.

Non-adherence to medication is associated with a significantly greater risk for violence (Arango *et al.* 2006; Ascher-Svanum *et al.* 2006; Swartz *et al.* 1998). There is some evidence that clozapine improves treatment adherence in comparison to FG drugs (Rosenheck *et al.* 2000), through greater and more regular clinical supervision coinciding with mandatory blood testing. Adequate pharmacological treatment and frequent outpatient clinic attendance reduce the risk of offending (Van Dorn *et al.* 2011). However, while it may be that regular supervision reduces the risk, it may equally be that it is those patients who at the outset are better able to comply with increased and more regular supervision and also more able to submit to the rigours of clozapine monitoring, who then show the greatest improvements. However, even when the frequency and intensity of monitoring is identical in clozapine and olanzapine treatment, clozapine-treated patients improveD more (Potkin *et al.* 2003). Thus, the limited evidence suggests that increased contact associated with clozapine treatment alone may not explain the greater efficacy of clozapine compared to other medications.

It may be that patients on clozapine experience fewer side-effects or that the side-effects they experience are better tolerated, monitored or managed (Leucht *et al.* 2009*a*, *b*; Ravanic *et al.* 2009). However, adverse effects were rarely discussed or investigated in the vast majority of studies reviewed. This is a serious limitation, given that it is clozapine's side-effect profile that may in part contribute to its advantage over other antipsychotics, and that clozapine is associated not only with many common side-effects (Essali *et al.* 2009) but also and more unusually some potentially life-threatening adverse effects (Manu *et al.* 2011). Certainly side-effects and perceived burden influences patients' compliance, which in turn influences a variety of other behaviours including emergency room use and hospitalization (Kim *et al.* 2010; Swanson *et al.* 2004; Topiwala & Fazel, 2011). Furthermore, extra-pyramidal and in particular, Parkinsonian side-effects, are predictors of suicidal behaviour (Potkin *et al.* 2003).

Regular compliance with SG antipsychotic medication is less likely to be associated with illicit drug misuse (Swanson *et al.* 2008*b*), probably the greatest single risk factor for aggression and violence in schizophrenia. Clozapine may limit the use of cannabis (Brunette *et al.* 2011), alcohol (Chau *et al.* 2010; Green *et al.* 2008, 2011), both combined (Green *et al.* 2003) and poly-substance abuse including cocaine (Zimmet *et al.* 2000) in comparison to FG and other SG antipsychotics. It even appears that clozapine treatment is associated with reduced cigarette smoking (McEvoy *et al.* 1999), although this remains contentious (de Leon *et al.* 2005).

Finally, cognitive deficits are linked to the risk of violence in schizophrenia. Krakowski & Czobor, 2011) found that executive function at baseline predicted later aggression in schizophrenia, although the authors also found that olanzapine, rather than haloperidol or clozapine, was associated with better cognitive outcomes (Krakowski *et al.* 2008). The findings in relation to clozapine are more mixed. There is some evidence linking it to improvements in verbal fluency

(Hagger *et al.* 1993; Meltzer & McGurk, 1999), attention (Grace *et al.* 1996; Meltzer & McGurk, 1999) and perceptual and motor processing (Grace *et al.* 1996; Hagger *et al.* 1993; Lee *et al.* 1999), although no direct link has been shown with the risk of aggression or violence. By way of contrast, others (e.g. Bilder *et al.* 2002) have suggested that clozapine's ability to improve cognition is only very modest and certainly not superior of other SG agents.

Due to the small number and inconsistent methodology of studies we were unable to perform a meta-analysis and unable to test for publication bias. It is therefore important to recognize the potential for a bias within the available literature. Studies which report favourable results, particularly intervention studies are more likely to be published than those with negative findings. Furthermore, the link between schizophrenia and violence is complex. Many factors associated with schizophrenia are also independently linked to the risk for violence. It is widely established that confounding variables such as young age, early onset of illness, co-morbid substance misuse or personality pathology all increase the risk of violence in patients with schizophrenia, and most probably in other mental illnesses. Few of the studies reviewed have attempted to assess or establish the presence of many of these features.

Clinical implications

In conclusion, clozapine is an effective antipsychotic for the treatment of psychotic symptoms and for the management of aggressive and violent behaviour in patients with schizophrenia, and other psychiatric disorders. It may be, however, that the advantage that clozapine appears to offer in terms of reducing the risk of violence is most prominent in those with true treatment resistance or treatment complexity,al though clozapine has principally been tested in these groups. Given the huge scale and cost of violent behaviour to patients as individuals, their families and caregivers and society at large, we urgently need to establish the best and most effective treatment for this aspect of the disorder. In the meantime, prescribers must remain mindful of the cost–benefit analysis, principally with regard to the potentially serious long-term adverse effects of clozapine treatment, carefully weighing these up with their patient before deciding to prescribe.

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