Clozapine is gold standard, but questions remain

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In their recent publication, Frogley and colleagues have reviewed the evidence indicating that clozapine treatment reduces aggressive behaviour in patients with schizophrenia, and perhaps with other disorders as well (Frogley et al. 2012). Although randomized controlled trials testing this anti-aggressive effect are relatively scarce, the evidence based on many studies supports it. There is general agreement on the superiority of clozapine’s anti-aggressive effect in schizophrenia, as reflected for example in published expert consensus guidelines (Kane et al. 2003, p. 38) and in standard textbooks (Volavka et al. 2012). However, there are issues that are not quite as clear.

Failure to respond to clozapine is one of these issues. In the general population of schizophrenia patients with treatment-resistant illness, only about 50% of patients respond to clozapine (Lieberman et al. 1994). The proportion of responders to clozapine in the treatment of aggression in schizophrenia has not been reliably established, but it is clear that not all patients will respond. The data published by Krakowski et al. (2006) probably represent the most robust support for the anti-aggressive superiority of clozapine over other antipsychotics in schizophrenia. The statistical analyses used in that paper (Krakowski et al. 2006) were not designed to define the outcome in dichotomous terms (response vs. non-response). However, the published interquartile ranges strongly suggest that non-responders to clozapine were present. Similar variability of response to clozapine was observed in other studies. The causes of this variability of response are not well understood.

In a follow-up paper, Krakowski & Czobor (2012) demonstrated that the superiority of clozapine was probably not due to its effect on executive functioning. The variability of response is therefore apparently attributable to other factors than cognitive performance. One reason for this variability is that aggressive behaviour in schizophrenia is heterogeneous in origin. There are numerous pathways that lead to the development of aggressive behaviour in schizophrenia. Elements of these pathways include factors such as genotype, childhood maltreatment, conduct disorder, comorbid antisocial personality disorder/psychopathy, development of psychotic symptoms, substance abuse, non-adherence to treatment, and stressful experiences in adult life (Volavka & Citrome, 2011).

Analyses of the data obtained in the context of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project (Lieberman et al. 2005) provided important insights into the role of conduct disorder in these pathways. At baseline, CATIE assessed the prevalence of violent behaviour during the preceding 6-month period in 1410 schizophrenia patients. During that period, violence was about twice as likely to occur in patients with a history of childhood conduct problems, such as starting fights in school, running away from home, and early substance abuse (Swanson et al. 2008b).

Furthermore, the history of childhood antisocial conduct affected clinical correlates of violence in adult schizophrenia patients. Positive psychotic symptoms (higher PANSS positive scores) were significantly associated with violence only in patients without childhood antisocial history. In contrast, among those with antisocial conduct history, violence risk was elevated irrespective of psychotic symptoms (Swanson et al. 2008b).

At CATIE baseline, the patients were randomly assigned to perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone and their symptomatology and violent behaviour were studied prospectively. The longitudinal prospective analysis of the first 6 months of treatment found that adherence with antipsychotic medications was associated with
significantly reduced violence only in the group without a history of conduct problems. In the conduct problems group, violence remained higher and did not significantly differ between patients who were adherent with medications and those who were not (Swanson et al. 2008a). These results were consistent with the baseline findings described above (Swanson et al. 2008b). They were also consistent with other work (Hodgins et al. 2005; Nolan et al. 1999, 2003).

Clozapine was not one of the drugs tested in this phase of CATIE. However, these results, if replicated for antipsychotics including clozapine, may have general implications for antipsychotic treatments of aggression in schizophrenia. Many patients with schizophrenia commit assaults that are not directly linked to psychosis (Nolan et al. 2003). Some of these patients can be identified by a history of conduct disorder.

It is possible that a proportion of those failing to respond to clozapine, seen in previous studies as well as in clinical practice, developed in patients with a history of conduct problems. It seems that obtaining a history of conduct disorder may become a useful component of research design and clinical practice dealing with aggressive schizophrenia patients. Patients with this history who fail to respond to clozapine are candidates for psychosocial treatments using cognitive behavioral therapy and other components (Haddock et al. 2009; Yates et al. 2010).

Of course, there are other possible reasons for failure to respond to clozapine, such as genetic factors influencing the rate of clozapine biotransformation (Jaquenoud et al. 2009), or non-adherence. Conversely, pharmacokinetic interactions can result in dangerously elevated plasma levels of clozapine. For these reasons, monitoring clozapine plasma levels in clinical practice is strongly recommended (Hienke et al. 2011).

Treatment persistence (time to discontinuation) with clozapine is longer in comparison with other antipsychotics; nevertheless, approximately 50% of the patients will discontinue clozapine after about 10 months (McEvoy et al. 2006; Moisan & Gregoire, 2010). The reasons for discontinuation are not completely clear. A study using pharmacy computer records compared reasons for discontinuation of clozapine and of long-acting injection of risperidone (Taylor et al. 2009). Adverse effects and death were more common reasons for discontinuation of clozapine than of risperidone. The most frequent reason for discontinuing clozapine was the patient’s decision (47.8%). In a retrospectively studied sample of patients who discontinued clozapine, the majority of patients discontinued because of their own decision or because of non-compliance with medical procedures such as blood sampling (Pai & Vella, 2011). Patient decision also accounted for most of the clozapine discontinuations in the CATIE study (McEvoy et al. 2006).

It seems that nobody asked the patients who decided to discontinue clozapine why they did so. Adverse effects were listed as a separate category among the reasons for discontinuation in these investigations (McEvoy et al. 2006; Pai & Vella, 2011; Taylor et al. 2009). Nevertheless, it is possible that some of the patients’ decisions to discontinue were driven by adverse effects that were not reported, or that were reported but considered relatively unimportant by raters who had to assign a reason to the discontinuation.

It is possible that some of the decisions to discontinue clozapine are due to fluctuations of insight. A small study has demonstrated that clozapine treatment improves the awareness of illness (Pallanti et al. 1999), but it is not clear how stable that improvement is over time. In general, insight is well known for playing a major role in treatment outcome as well as in antipsychotic medication adherence and persistence (David, 1990; Wiffen et al. 2010). This is not surprising: patients who do not believe that they are ill frequently do not think that they need medication. In a study of first-episode schizophrenia, schizoaffective disorder, and schizophreniform disorder treated with haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone (Kahn et al. 2008), the levels of insight (assessed by the PANSS ‘insight’ item) at several time points were predictive of medication adherence (Czobor et al. unpublished observations). Future research may show if these results will generalize to clozapine.

When clozapine cannot be used, or when its effect is inadequate, alternative treatments are available for the general populations of schizophrenia patients (Citrome & Volavka, 2011; Volavka et al. 2012). Results that are specific for first-episode schizophrenia patients were obtained by analysing the levels of hostility (assessed by the PANSS ‘hostility’ item) in the study cited above (Kahn et al. 2008). The results showed that olanzapine was superior to haloperidol, quetiapine and amisulpride in reducing hostility during the first 3 months of treatment (Volavka et al. 2011). If replicated, this superiority would suggest that olanzapine may be a suitable alternative to clozapine in the treatment of hostility (and, by implication, of overt aggression) in first-episode psychoses.

Current treatment strategies for the management of aggressive behaviour in schizophrenia do not stress the importance of insight. This is unfortunate. Insight is modifiable, and psychosocial interventions,
including psychoeducation, cognitive behavioural therapy, and family intervention are available (Velligan et al. 2010).

Future studies of anti-aggressive effects of clozapine in schizophrenia should use the information contributing to the aetiological heterogeneity of violence to explain the heterogeneity of treatment outcome. Thus, history of conduct disorder, and perhaps of child abuse (Bennouna-Greene et al. 2011), should be included as independent variables. The role of insight in persistence and adherence with clozapine treatment deserves further study.

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References


