

Reasons for discontinuing clozapine: matched, case–control comparison with risperidone long-acting injection

David M. Taylor, Petrina Douglas-Hall, Banke Olofinjana, Eromona Whiskey and Arwel Thomas

Background

Clozapine has a range of serious adverse effects that may give rise to an increased risk of death.

Aims

To compare reasons for discontinuation of clozapine with reasons for discontinuation of risperidone long-acting injection in age-matched individuals treated in the same clinical environment.

Method

Comparison of patients receiving clozapine and an age-matched control group receiving risperidone injection.

Results

We established outcome for 529 consecutive patients receiving clozapine and 250 receiving risperidone (161 discontinuers from each group were compared). Adverse effects (odds ratio OR=2.19, 95% CI 1.31–3.67) and death (OR=7.0, 95% CI 2.09–23.5) were more commonly observed

as reasons for discontinuation of clozapine than of risperidone. Clozapine was less likely to be withdrawn because of ineffectiveness than was risperidone (OR=0.034, 95% CI 0.01–0.14). Standardised mortality ratio (SMR) was significantly raised for patients receiving clozapine (SMR=4.17, 95% CI 2.78–6.26). Pneumonia was the most common single cause of death.

Conclusions

Clozapine use in patients with severe mental illness was associated with a significantly increased risk of death compared with that for the general population. Causation could not be established. Adverse effects and death are common causes of clozapine discontinuation.

Declaration of interest

D.M.T. has received research funding and honoraria from Janssen-Cilag, Novartis and IVAX.

Clozapine remains the treatment of choice for refractory schizophrenia despite its association with a wide range of adverse effects, both trivial and life-threatening. Clozapine is well known to cause blood dyscrasias¹ but it is also associated with other serious adverse effects such as seizures,² intestinal obstruction,³ myocarditis,⁴ diabetes,⁵ thromboembolism and cardiomyopathy.⁶

The frequency and variety of these effects might be expected to afford a relatively higher mortality in those receiving clozapine compared with other antipsychotics. However, studies suggest that clozapine reduces overall mortality⁷ (at least when compared with periods when not taking clozapine),⁸ probably because it lowers suicide risk.⁹

In a recent study,¹⁰ we found that death was a common cause of clozapine treatment cessation. We wanted to compare reasons for discontinuation with another second-generation antipsychotic but were aware that covert non-adherence might confound our results (non-adherence with clozapine in responsive patients results in relapse and so is readily confirmed). In our study we compared reasons for stopping clozapine with a matched cohort of patients stopping risperidone long-acting injection.

Method

This study was approved by the South London and Maudsley Drug and Therapeutics Committee as part of its on-going audit programme. We used pharmacy computer records to determine all patients registered in to receive clozapine in the South London and Maudsley NHS Foundation Trust between March 2002 and October 2006 and identified all patients ceasing treatment during this period. Each person who discontinued clozapine (clozapine group) was matched by age and gender at discontinuation with a person who discontinued risperidone long-acting injection

without knowledge of reason for discontinuation. Details of those who discontinued risperidone were obtained from our database of 277 patients developed for a previous study.¹¹ Risperidone patients began treatment in or after August 2002 and ceased treatment before October 2004.

We did not perform a power calculation but used all reliable data available to us at the time. Patients in both cohorts received standard care (i.e. there was no extraneous intervention), were largely drawn from the local population and all were prescribed their antipsychotics by secondary-care psychiatrists. A small proportion in each group (<10%) were tertiary referrals.

We obtained from case notes data on ethnicity, diagnosis, duration of treatment and reason for discontinuation. We categorised reason for discontinuation as: patient decision (partial or non-adherence, or patient request or refusal); adverse effects (clinician decision to withdraw because of unacceptable side-effects); ineffective (clinician assessment of inadequate effect); death; or other. Where death was the cause of discontinuation but the exact cause of death unclear, we obtained death certificates from the public record office.

We also established mortality rates for all those known to have been treated with either drug during the observation periods stated. Study cohorts' expected mortality rates were calculated using age-specific population mortality rates for 2002 supplied by the UK Office for National Statistics.¹² Standardised mortality ratios (SMRs) were calculated using the indirect standardisation method.

Results

During the study period, 592 patients were registered to receive clozapine, 368 continued and 224 were deregistered (63 did not

Characteristic	Clozapine (n=161)	Risperidone (n=161)
Age at discontinuation, years: mean (s.d.) (range)	40.0 (12.6) (18–83)	39.9 (13.1) (18–83)
Gender		
Male	99	99
Female	62	62
Ethnicity		
White	72	61
Black (African/Caribbean)	61	79
Asian	13	9
Mixed	15	12
Diagnosis		
Schizophrenia	131	119
Schizoaffective disorder	17	12
Bipolar disorder	8	19
Other	5	11
Duration of treatment with clozapine/risperidone, months: mean (s.d.) (range, median)	12.3 (18.6) (0.25–100, 3.0)	5.9 (8.7) (0.5–46, 3.0)
Dose at cessation, mg/day: mean (s.d.) (range)	360 (159) ^a (12.5–1000)	34.5 (12.2) ^b (12.5–75)
Last recorded plasma level, mg/l: mean (s.d.) (range)	0.36 (0.39) ^c (0–2.61)	N/A
N/A, not applicable.		
a. Dose known for 85 of 161 patients		
b. Every 2 weeks.		
c. Plasma level recorded for 132 of 161 patients; of these, 27 (20.5%) had plasma levels of 0.0–0.05 mg/l, indicating probable non-adherence.		

start clozapine or left our services during the study period). Thus, 161 patients received clozapine for at least 1 week and later discontinued. In total, 277 patients received at least one injection of risperidone, of whom 27 were lost to follow-up. Of the remaining 250, 184 discontinued and 161 were matched to patients who had discontinued clozapine (Table 1). Reasons for drug discontinuation for each group are shown in Table 2.

Mean age of those who died on clozapine was 49.2 years (s.d.=14.5, range 30–83), mean duration of treatment was 38.2 months (s.d.=29.5, range 3–100). Mean last recorded dose was 412 mg/day (s.d.=141, range 100–650) and mean last recorded clozapine level (known for 18 of 21 patients) was 0.48 mg/l (s.d.=0.31, range 0.02–1.12). Mean plasma level in those surviving (known for 114 of 140 patients) was 0.34 mg/l (s.d.=0.41, range 0.0–2.61); 25 of these had levels (0.0–0.05 mg/l) suggesting non-adherence. The deaths occurring in people receiving risperidone were in patients aged 48, 65 and 81 years. Duration of treatment with risperidone injection was 40 months, 2 weeks and 38 months respectively. We did not record duration of illness for study participants but mean duration of illness in the risperidone cohort was about 11 years.¹¹

Cause of death in clozapine patients was: pneumonia (n=5), lung carcinoma (n=3), other carcinoma (n=2), myocardial

infarction (n=2), cerebrovascular accident (n=2), clozapine overdose (n=2), gastrointestinal haemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during restraint (n=1) and sepsis (n=1). There was no evidence of neutropenia or agranulocytosis in any patients at the time of death. Cause of death was established from case notes in 8 patients and death certificate in the remaining 13. Cause of death in those taking risperidone was: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexplained death (n=1). There were no deaths in the unmatched patients discontinuing risperidone.

Overall, we established outcome for 529 patients (mean age in March 2002, 36.4 years (s.d.=11.6)) receiving clozapine for at least a week during a period of 4.67 years and 250 patients (mean age 38.6 years, (s.d.=13.8)) receiving at least one risperidone injection during a period of 2.25 years. Mortality rate was 8.5 (95% CI 5.53–13.07) per 1000 patient-years for clozapine patients and 5.3 per 1000 patient-years (95% CI 1.7–16.61) for those receiving risperidone injection. Expected mortality rates were 2.04 per 1000 patient-years and 3.51 per 1000 patient-years respectively. Standardised mortality ratios were 4.17 (95% CI 2.78–6.26) for clozapine and 1.51 (95% CI 0.49–4.65) for risperidone patients.

Discussion

Reasons for discontinuation differed between clozapine and risperidone injection: adverse effects and death were more commonly recorded as reasons of discontinuation with clozapine and ineffectiveness was more often reported with risperidone. These findings have important implications for practice.

Mortality rates and cause of death

We also found that clozapine use was associated with an increased risk of death. Age at death was very low and mortality rate was higher for clozapine patients than that expected for an age-matched UK general population. Our observed mortality rate for clozapine (8.5 per 1000 patient-years) is similar to that seen in other studies.^{8,9} The contribution of schizophrenia to the observed increased mortality in this study cannot be discounted,¹³ although the risperidone group did not show an increased SMR (although the small number of deaths did not allow accurate determination of SMR).

It is probable that both schizophrenia and the use of anti-psychotics each contribute to the previously observed increased mortality, although individual contributions are difficult to discern.¹⁴ It has been suggested that the mortality gap between the normal population and those with schizophrenia is growing, possibly because of increased use of atypical drugs.¹⁵

Cause of death suggests some contributory role for clozapine: six cardiovascular deaths may have been associated with clozapine's metabolic effects,¹⁶ although, again, the influence of schizophrenia itself on cardiovascular mortality is clearly important.¹⁷ In addition, five patients died of a primary pneumonia, a condition previously described as a cause of death

Reason	Clozapine (n=161) n (%)	Risperidone (n=161) n (%)	OR (95% CI)	McNemar's χ^2 , d.f.=1
Patient's decision	77 (47.8)	64 (39.7)	1.41 (0.89–2.21)	2.195 (P=0.139)
Adverse effects	57 (35.4)	32 (19.9)	2.19 (1.31–3.67)	9.328 (P=0.0023)
Ineffective	3 (1.9)	59 (36.6)	0.034 (0.01–0.14)	52.267 (P<0.0001)
Death	21 (13.0)	3 (1.9)	7 (2.09–23.5)	13.5 (P=0.0003)
Other	3 (1.9)	3 (1.9)	–	–

in clozapine patients⁸ and one known to be more common in elderly people receiving atypical antipsychotics.¹⁸ However, pneumonia is not a widely accepted adverse effect of clozapine,⁷ except perhaps as a result of aspiration of saliva and even then only in rare cases.¹⁹ It is possible that smoking plays a part. Smoking may increase the incidence of bronchial infection, leading to an acute reduction in smoking frequency which then provokes clozapine toxicity^{20,21} and which may subsequently allow the development of pneumonia (patients are more sedated and less mobile). We were unable to establish smoking status for any of our participants because case notes are unreliable sources of this information. Clozapine is known to reduce smoking behaviour²² so it seems unlikely that smoking was more prevalent in the clozapine group than the risperidone group. None the less, the observation that three patients died of lung cancer suggests a significant prevalence of smoking in the clozapine group.

Study limitations

Limitations of our method include the potentially unreliable nature of data derived from case notes and the failure to collect information on other factors likely to affect outcomes (smoking status, concurrent physical illness, illness duration). Indeed, as clozapine is often reserved for treatment of longstanding, refractory illness, duration of illness and exposure to antipsychotics are likely to be relatively greater.

Clinical implications

The number and causes of death in the clozapine group suggest an important role for prevention and management of physical illness. Testing for obesity, dyslipidaemia, hypertension and diabetes are clearly essential but studies show that physical monitoring is rarely undertaken in people taking antipsychotics,^{23,24} although interventions to improve monitoring can be effective.²⁵ Similarly, smoking cessation should be encouraged and assistance offered. Moreover, given the findings of this study, any bronchial infection occurring in a patient on clozapine should provoke immediate and aggressive treatment. Consideration might also be given to the addition of other drugs (e.g. aripiprazole) to clozapine, which might mitigate its adverse metabolic effects.²⁶

Our study emphasises the need for prudence in the choice of antipsychotic and the necessity for close physical monitoring of patients receiving antipsychotics, particularly clozapine. It also highlights the problems faced by clinicians who feel obliged to use clozapine because of its effectiveness, while being aware of the likelihood of severe adverse effects.

David M. Taylor, MSc, PhD, MRPharmS, Pharmacy Department, South London and Maudsley NHS Foundation Trust, and Division of Pharmaceutical Sciences, King's College London; **Petrina Douglas-Hall**, BPharm, MRPharmS, **Banke Olofinjana**, BPharm, MRPharmS, **Eromona Whiskey**, BPharm, MRPharmS, **Arwel Thomas**, MPharm, MRPharmS, Pharmacy Department, South London and Maudsley NHS Foundation Trust, UK

Correspondence: David M. Taylor, Pharmacy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK. Email: David.Taylor@slam.nhs.uk

First received 2 Mar 2008, final revision 9 Jul 2008, accepted 6 Aug 2008

References

- Atkin K, Kendall F, Gould D, Freeman H, Lieberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**: 483–8.
- Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. *Neurology* 1991; **41**: 369–71.
- Townsend G, Curtis D. Case report: rapidly fatal bowel ischaemia on clozapine treatment. *BMC Psychiatry* 2006; **6**: 43.
- Killian JG, Kerr K, Lawrence C, Celermajor DS. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; **354**: 1841–5.
- Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. *Arch Gen Psychiatry* 2001; **58**: 1172–6.
- Hagg S, Spigset O, Soderstrom TG. Association of venous thromboembolism and clozapine. *Lancet* 2000; **355**: 1155–6.
- Sernyak MJ, Desai R, Stolar M, Rosenheck R. Impact of clozapine on completed suicide. *Am J Psychiatry* 2001; **158**: 931–7.
- Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology* 1997; **8**: 671–7.
- Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; **60**: 82–91.
- Atkinson JM, Douglas-Hall P, Fischetti C, Sparshatt A, Taylor DM. Outcome following clozapine discontinuation: a retrospective analysis. *J Clin Psychiatry* 2007; **68**: 1027–30.
- Young CL, Taylor DM. Health resource utilization associated with switching to risperidone long-acting injection. *Acta Psychiatr Scand* 2006; **114**: 14–20.
- Office for National Statistics. *Mortality Statistics, 2002. Series DH1, no. 35*. ONS, 2003.
- Osby U, Correia N, Brandt L, Ekbohm A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000; **45**: 21–8.
- Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Schizophrenia, neuroleptic medication and mortality. *Br J Psychiatry* 2006; **188**: 122–7.
- Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; **64**: 1123–31.
- Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000; **157**: 975–81.
- Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *J Clin Psychiatry* 2004; **65**: 715–20.
- Knol W, van Marum RJ, Jansen PA, Souverein PC, Schobben AF, Egberts AC. Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc* 2008; **56**: 661–6.
- Hinkes R, Quesada TV, Currier MB, Gonzalez-Blanco M. Aspiration pneumonia possibly secondary to clozapine-induced sialorrhea. *J Clin Psychopharmacol* 1996; **16**: 462–3.
- Derenne JL, Baldessarini RJ. Clozapine toxicity associated with smoking cessation: case report. *Am J Ther* 2005; **12**: 469–71.
- Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol* 2002; **17**: 141–3.
- Procyshyn RM, Tse G, Sin O, Flynn S. Concomitant clozapine reduces smoking in patients treated with risperidone. *Eur Neuropsychopharmacol* 2002; **12**: 77–80.
- Paton C, Esop R, Young C, Taylor D. Obesity, dyslipidaemias and smoking in an inpatient population treated with antipsychotic drugs. *Acta Psychiatr Scand* 2004; **110**: 299–305.
- Taylor D, Young C, Esop R, Paton C, Walwyn R. Testing for diabetes in hospitalised patients prescribed antipsychotic drugs. *Br J Psychiatry* 2004; **185**: 152–6.
- Barnes TR, Paton C, Hancock E, Cavanagh MR, Taylor D, Lelliott P. Screening for the metabolic syndrome in community psychiatric patients prescribed antipsychotics: a quality improvement programme. *Acta Psychiatr Scand* 2008; **118**: 26–33.
- Henderson DC, Kunkel L, Nguyen DD, Borba CP, Daley TB, Louie PM, et al. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. *Acta Psychiatr Scand* 2006; **113**: 142–7.