Rates of clozapine-associated myocarditis and cardiomyopathy: aystematic review and meta-analysis

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Background

Clozapine is the most effective medication for treatment refractory schizophrenia, but is associated with cardiac adverse drug reactions (ADRs). Myocarditis and cardiomyopathy are the most serious ADRs. However reported rates of these conditions vary in the literature. We systematically reviewed and meta-analysed the event rates of clozapine associated myocarditis and cardiomyopathy, and the absolute death rates and case fatality rates.

Methods

PubMed, EMBASE and PsycINFO were searched for studies that reported on the incidence of cardiomyopathy or myocarditis in people exposed to clozapine. Data were meta-analysed using a random effects model, with subgroup analysis on study size, time frame, region, quality, retrospective vs prospective and definition of myocarditis or cardiomyopathy.

Results

28 studies of 258,957 people exposed to clozapine were included. The event rate of myocarditis was 0.007 (95%CI 0.003-0.016), absolute death rate 0.0004 (95%CI 0.0002-0.0009) and case fatality rate 0.127 (95%CI 0.034-0.377). The cardiomyopathy event rate was 0.006 (95%CI 0.002-0.023) and absolute death rate 0.0003 (95%CI 0.0001-0.0012) and case fatalities rate 0.078 (95%CI 0.018-0.285). Few included studies provided information on criteria for diagnosis of myocarditis and cardiomyopathy.

Figure 1: PRISMA diagram

Table 1. Meta-analysis and sensitivity analysis of clozapine-associated myocarditis

Analysis	Number of samples	Incidence	Effect size (event rate with 95%CI)			Between sample heterogeneity
			Point estimate	Lower limit	Upper limit	
Rates of clozapine-associated myocarditis	24	0.7%	0.007	0.003	0.016	Q=1,438.6 df(Q)=23 p<0.01 I ² =98%
Absolute death rates from clozapine-associated myocarditis	18	0.04%	0.0004	0.0002	0.0009	Q=59.3 df(Q)=17 p<0.01 I ² =71%
Case fatality rate of clozapine-associated myocarditis	12	12.7%	0.127	0.034	0.377	Q=110.4 df(Q)=11 p<0.01 I ² =90%
Sensitivity analysis of rate of clozapine-associated myocarditis						
Restricted to high quality samples	14	1.3%	0.013	0.005	0.030	Q=119.9 df(Q)=13 p<0.01 I ² =89%
Restricted to studies reporting at least one event	18	0.7%	0.007	0.003	0.019	Q=1,430.3 df(Q)=17 p<0.01 I ² =98.8%

Table 2. Meta-analysis and sensitivity analysis of clozapine-associated cardiomyopathy

Analysis	Number of samples	Incidence	Effect size (event rate with 95%CI)			Between sample heterogeneity
			Point estimate	Lower limit	Upper limit	
Rates of clozapine-associated cardiomyopathy	16	0.6%	0.006	0.002	0.023	Q=836.9 df(Q)=15 p<0.01 I ² =98%
Absolute death rates from clozapine-associated cardiomyopathy	17	0.03%	0.0003	0.0001	0.0012	Q=44.2 df(Q)=16 p<0.01 I ² =64%
Case fatality rate of clozapine-associated cardiomyopathy	12	7.8%	0.078	0.018	0.285	Q=31.8 df(Q)=11 p<0.01 I ² =65%
Sensitivity analysis of rate of clozapine-associated myocarditis						
Restricted to high quality samples	10	0.8%	0.008	0.002	0.029	Q=91.5 df(Q)=9 p<0.01 I ² =90%
Restricted to studies reporting at least one event	12	0.7%	0.007	0.002	0.032	Q=834.0 df(Q)=11 p<0.01 I ² =99%

Conclusions

Clarity of definition for myocarditis remains a challenge. Monitoring for myocarditis is warranted in the first 4 weeks, and treatment of comorbid metabolic syndrome and diabetes may reduce the risk of cardiomyopathy. The risks of myocarditis and cardiomyopathy are low and should not present a barrier to people with treatment refractory schizophrenia being offered a monitored trial of clozapine.