

# Echocardiography and clozapine: Is current clinical practice inhibiting use of a potentially life-transforming therapy?

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Approximately 33% of patients with schizophrenia are treatment-refractory, yet clozapine remains underused, even though it is the most effective treatment.<sup>1,2</sup> One barrier is routine echocardiography, which in Australia is performed before clozapine initiation, six months afterwards and then annually.<sup>3</sup> Elsewhere, such as in New Zealand, routine echocardiography is generally restricted to the initiation of therapy, while in the UK, it is not routine practice at all. Importantly, the latest guidelines from The Royal Australian and New Zealand College of Psychiatrists (RANZCP) suggest routine annual echocardiography adds little to the detection of cardiomyopathy.<sup>4</sup> We therefore review the evidence for routine echocardiography. This is particularly relevant to general practitioners (GPs) as they become more involved in managing patients on clozapine through shared-care arrangements.<sup>1</sup>

Common side effects of clozapine include metabolic syndrome, hypersalivation, constipation and sedation. Of particular concern are the potentially life-threatening side effects of myocarditis, cardiomyopathy and agranulocytosis. In spite of this, long term follow-up indicates that patients on clozapine have a lower risk of premature mortality than either those on other antipsychotics or those not taking regular medication, largely by reducing the

rates of suicide.<sup>5</sup> Importantly, the death rate from cardiovascular disease is no different for clozapine than for other antipsychotic medication despite its metabolic side effects.

Approximately 3% of Australians on clozapine develop myocarditis, a rate some 30 times higher than elsewhere, apart from New Zealand.<sup>6</sup> The discrepancy in rates cannot be explained by Australia's regular use of echocardiography, given that myocarditis mostly occurs within the first four weeks of commencing clozapine and, therefore, would not be detected by routine echocardiography at the six-month follow-up or thereafter. Routine echocardiography is only useful at baseline, in combination with monitoring of troponin and C-reactive protein (CRP) 7, 14, 21 and 28 days after starting clozapine.<sup>7</sup> This protocol had a sensitivity of 100%, provided infective illness was excluded, and troponin and CRP were measured in the presence of myocarditis symptoms.<sup>7</sup>

The reported incidence of clozapine-related cardiomyopathy is lower than that of myocarditis, ranging from 0.05% to 0.22%, and is similar worldwide.<sup>3</sup> The mean time from commencement of clozapine to first symptoms of cardiomyopathy is 14 months. Most cases occur within six to nine months of clozapine commencement.<sup>8</sup> Mortality from cardiomyopathy ranges from 12.5% to 24%.<sup>8</sup> However, it is often difficult

to establish causality, given the increased prevalence of other risk factors, including comorbid metabolic syndrome, diabetes and alcohol or substance abuse, in people with treatment-refractory schizophrenia, as well as the absence of markers that indicate clozapine as the cause.<sup>3</sup>

The effectiveness, both clinical and financial, of regular echocardiography in the monitoring of patients on clozapine is debatable in the absence of symptoms such as exertional dyspnoea, tachypnoea or cough. In a follow-up study of 159 patients on clozapine, only three cases of myocarditis were identified. All three cases occurred within the first month of treatment and were suspected on clinical grounds before an echocardiogram was performed.<sup>3</sup> Only one case of possible cardiomyopathy was identified through echocardiography. The cost of detecting one clozapine-related case of cardiac pathology was estimated to be between AU\$200,000 and AU\$1 million.<sup>3</sup> A recent systematic review of clozapine-induced cardiomyopathy found no evidence to support routine follow-up screening with echocardiography for asymptomatic patients on clozapine.<sup>8</sup>

At a clinical level, non-compliance with monitoring was the reason for discontinuation of clozapine in more than a third of patients in one Australian study.<sup>9</sup> Although the contribution of echocardiography to discontinuations may

be less than that resulting from routine blood monitoring, the practice of annual echocardiography has been described as costly, time-consuming and logistically difficult.<sup>3</sup>

The management of asymptomatic patients who are identified on routine echocardiography with mild cardiomyopathy is also unclear. For example, current guidelines for the management of heart failure do not specifically address clozapine-associated cardiomyopathy, particularly asymptomatic cardiomyopathy, although the combination of a beta-blocker and an angiotensin converting enzyme inhibitor may limit some adverse effects of clozapine.<sup>10</sup> The clinician is faced with a dilemma when an echocardiogram suggests minor cardiac dysfunction in an otherwise asymptomatic individual. In this scenario, few practitioners would cease clozapine in people who have treatment-resistant schizophrenia, further highlighting the redundancy of routine echocardiography.

In conclusion, excessive diagnostic testing is not only a burden to patients, but creates an unnecessary expense to stretched healthcare budgets. The latest RANZCP guidelines should go some way to remedy this.<sup>4</sup> These recommend

routine echocardiography at baseline, with echocardiograms only being repeated if clinically indicated, or following abnormal serum CRP and troponin results.<sup>4</sup> This should be in the context of routine history taking and physical examination for evidence of relevant risk factors or cardiovascular disease.

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Competing interests: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

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