Psychiatry Research 282 (xxxx) xxxx

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

Clozapine and cardiotoxicity – A guide for psychiatrists written by cardiologists

Rishi K. Patel[a,*], Alice M. Moore[b], Susan Piper[c], Mark Sweeney[a], Eromona Whiskey[d], Graham Cole[a], Sukhi S. Shergill[e], Carla M. Plymen[a]

[a] Department of Cardiology, Imperial College Healthcare NHS Trust, London, UK
[b] Department of Cardiology, Mater Dei Hospital, Malta
[c] Department of Cardiology, King's College Hospital, London, UK
[d] Pharmacy Department, Maudsley Hospital, UK
[e] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

ARTICLE INFO

Keywords:
Schizophrenia
Myocarditis
Cardiomyopathy
Pharmacotherapy
Psychosis

ABSTRACT

This review discusses the rare but potentially life-threatening cardiovascular side-effects of myocarditis and dilated cardiomyopathy associated with the use of Clozapine. The clinical presentation of these conditions is non-specific, making it difficult to both risk-stratify and identify patients who develop these consequences. This review aims to examine the proposed aetiologies, diagnostic approaches and subsequent management strategies of cardiotoxicity associated with clozapine use; offering guidance to psychiatrists and general physicians. Current evidence highlights the importance of accurate diagnosis to prevent premature and unnecessary cessation of clozapine. Guidance on monitoring and reintroduction of the drug is emerging and current practice recommends a combination of regular monitoring of biomarkers and imaging to make a diagnosis of cardiotoxicity although further work is needed to establish evidence-based guidelines.

1. Introduction

Treatment-resistant schizophrenia (TRS) affects 30% of those with schizophrenia and refers to those who do not respond to two or more antipsychotic agents. Clozapine is the only licensed agent for TRS and reduces symptoms of psychosis by 40%, significantly decreases psychiatric-related hospital admissions and reduces mortality in terms of suicidality (De Berardis et al., 2012; Siskind et al., 2017; Stroup et al., 2016). The effects on morbidity and mortality offer further benefits of improved societal and economic functioning (Fitton and Benfield, 1993).

Evidence shows that prescription rates of clozapine in eligible patients is low (Warnez and Alessi-Severini, 2014). Underuse is thought to arise from the side-effect profile and underlies a tendency to discontinue clozapine at the earliest sign of toxicity. A survey of practitioners familiar with clozapine prescribing guidelines identified the main barriers to initiating treatment as concerns over tolerability and compliance (Gee et al., 2014). Although the most frequently cited toxic side-effect of clozapine is agranulocytosis, there are well-established guidelines to facilitate monitoring of this. Cardiovascular side-effects, although rarer, include life-threatening myocarditis and dilated cardiomyopathy (De Berardis et al., 2012) but at present, no guidelines exist for their monitoring.

The British National Formulary (BNF) supports a tentative stance on clozapine use, recommending cautious use in those with pre-existing cardiac disease and avoidance in those with severe cardiac conditions. Whether all pre-existing cardiac diseases are considered contra-indications is not known, nor what defines a 'severe' condition. Given the increased frequency of comorbid cardiovascular disease in those with schizophrenia, a "by-the-book" approach automatically excludes a significant proportion of patients who might otherwise derive significant benefit from clozapine. Furthermore, the FIN11 study found that long term use of anti-psychotic drugs is associated with an overall lower mortality than placebo, with clozapine carrying the lowest mortality of all (Tiihonen et al., 2009).

This review article is written by cardiologists and focuses specifically on clozapine-induced cardiotoxicity, primarily manifesting as myocarditis and cardiomyopathy. Recent trials of novel antipsychotic agents have proven inconclusive in offering alternative options to clinicians, facilitating a resurgence of interest in ensuring all those who might benefit from clozapine receive it (Dunlop and Brandon, 2015). We will describe the known aetiologies, diagnosis and management of

* Corresponding author.
E-mail address: rishipatel@nhs.net (R.K. Patel).

https://doi.org/10.1016/j.psychres.2019.112491
Received 26 June 2019; Received in revised form 20 July 2019; Accepted 20 July 2019

cardiotoxicity associated with clozapine use; offering guidance to psychiatrists and general physicians, thereby hopefully supporting its increased use and preventing premature cessation of therapy where possible.

2. Methods

Literature searches were performed through PubMed and Cochrane databases using keywords including clozapine, schizophrenia, cardiomyopathy and myocarditis to identify manuscripts on the development or implementation of current guidelines and common clinical practice, including relevant individual clinical trials and older landmark studies.

3. Definitions & incidence

Myocarditis is defined as inflammation of the myocardium and tends to present acutely with a short prodrome of illness. Cardiomyopathy is characterised by structural abnormality of the left ventricle (LV) and can in fact be caused by myocarditis. It is however a much more chronic disease. Both can result in left ventricular systolic dysfunction associated with a fall in the left ventricular ejection fraction (LVEF) and both are associated with significantly increased morbidity and mortality.

The incidence of clozapine-induced myocarditis is ill-defined and estimated at 0.2–3% (Cook et al., 2015). Although it can occur at any time during treatment, the literature suggests that over 80% of cases developed within the first 4 weeks of treatment, thus occurs early on starting therapy (Bellissima et al., 2018; Kilian et al., 1999).

Clozapine-induced cardiomyopathy occurs less frequently, in less than 1 in 1000 patients (Longhi and Heres, 2017). It tends to manifest later during therapy, with onset of symptoms between 3 weeks to 4 years following initiation. One systematic review quoted an average of 14.4 months for symptoms to develop (Alawami et al., 2014).

4. Clozapine dosages in treatment-resistant schizophrenia

The current National Institute for Health and Care Excellence (NICE) guidelines for starting clozapine in TRS recommends incremental dose increases up to a minimum effective dose, usually between 250–400 mg/day. Current evidence on whether a dose-dependent relationship between clozapine and subsequent cardiotoxicity exists, is inconclusive: One review of myocarditis found that the median dose of clozapine at presentation was 250 mg/day (Bellissima et al., 2018). Another identified patients presenting with myocarditis whilst taking doses as low as 12.5 mg/day (Hill and Harrison-Woolrych, 2008). A systematic review of 26 individual cases of cardiomyopathy found the mean daily dose at presentation to be 360 mg, with a wide range between 125–700 mg (Alawami et al., 2014). Interestingly, the only study showing dose-related decreases in LVEF was in clozapine-treated rats but this study used concentrations above the recommended maximum daily dose in humans (Abdel-Wahab and Metwally, 2014). There is no clear evidence therefore, that the dose of clozapine has a direct effect on the risk of cardio-toxicity.

5. Risk factors

Several risk factors for developing clozapine-induced cardiotoxicity have been proposed: Rapid dose titration in the development of myocarditis, alongside increased age and concomitant use of sodium valproate was identified in one study, whilst another found a significant association with concomitant SSRI use (Ronaldson et al., 2012a; Youssef et al., 2016). Clozapine-induced cardiomyopathy was not associated with any specific risk factors in the latter study (Youssef et al., 2016). Nonetheless, there are no established specific risks and it is the authors' opinion that since myocarditis occurs early with the initiation of any causative drug, up-titration is more of a coincidence than a risk during this time period.

There is underlying significant cardiovascular risk in psychiatric patients (Brown et al., 2000; De Hert et al., 2011). A large meta-analysis of patients with severe mental illness found 10% to have at least one comorbid cardiovascular disease and identified significantly increased cardiovascular morbidity and mortality (Correll et al., 2017). This is likely to add an extra burden of risk to patients subsequently prescribed clozapine and highlights the importance of a holistic approach in any therapeutic strategy. A holistic approach could usefully include assessing for, and actively treating any baseline co-morbidity, such as cardiovascular or metabolic dysfunction – as part of a pre-clozapine work-up. Whilst it is established that antipsychotic use can induce adverse metabolic effects, it must also be remembered that effective treatment of the underlying psychiatric disease can lead to better uptake of therapy for concomitant cardiovascular conditions and subsequent decrease in long-term risk. This, in some patients, is the only way to manage and treat underlying cardiovascular disease.

6. Proposed mechanisms

The mechanism by which clozapine induces cardiotoxicity remains unclear but numerous hypotheses have been proposed, including IgE-mediated pathways, cytokine-driven responses and oxidative stress related to a hypercatecholaminergic state (Table 1) (Abdel-Wahab and Metwally, 2014, 2015; Kilian et al., 1999; Kluge et al., 2009; Pollmächer et al., 1996; Wang et al., 2008). Interestingly, interactions between free radicals, nitrogen oxide species and oxidative stress are also the best described mechanisms through which anthracycline drugs injure the myocardium during cancer therapy. This has been vigorously studied for over 30 years in these populations but the same cannot be said with regards to those on antipsychotic agents. It is intriguing that similar mechanisms may underpin both phenotypes and this might suggest that the diagnosis, management and long-term outcomes might perhaps be similar. Furthermore, cancer therapy can be regarded as just as life-saving as anti-psychotic therapy for TRS with its associated risk/benefit decisions.

Table 1
Proposed mechanisms of clozapine-induced cardiotoxicity.

Proposed mechanism	Evidence
Type 1 IgE-mediated acute hypersensitivity reaction	Killian et al., studies 23 cases of clozapine-induced cardiotoxicity and found both a peripheral eosinophilia and eosinophilic inclusions at endomyocardial cardiac biopsy in 5 patients with myocarditis and 1 patient with cardiomyopathy related to clozapine use.
Pro-inflammatory cytokines	Multiple studies of animal models of clozapine-induced cardiotoxicity have demonstrated an increase in plasma level of the pro-inflammatory cytokine TNF-α. Kluge replicated these results in a small randomised controlled trial of 30 patients. Abdel-Wahab also observed a decrease in the anti-inflammatory cytokine IL-10 in rodents with clozapine-induced cardiotoxicity.
Catecholamine and oxidative stress	Multiple studies in animal models also identified a rise in circulating catecholamines which correlated with myocardial inflammation. Use of beta-adrenergic blockade significantly attenuated these effects. One author inferred that the subsequent increased myocardial oxygen demand from the hypercatecholaminergic state will contributed to an increase production of free radicals which plays an important role in oxidative stress.

7. Signs and symptoms

The signs and symptoms of clozapine-induced cardiotoxicity are varied; there is no classical presentation.

7.1. Myocarditis

Typically, drug-induced myocarditis occurs early on exposure. It presents with a spectrum of features, from low-grade fever to fulminant cardiogenic shock and unheralded sudden death, though this is very uncommon. It presents similarly regardless of aetiology, with the commonest symptoms being fever, chest pain, new breathlessness and/or palpitations (Layland et al., 2009; Razminia et al., 2006). Signs are likewise varied and can even be absent unless in cardiogenic shock.

With mild symptoms, it is not unusual for many patients to experience myocarditis and be unaware until many years later, if at all. As such, 'asymptomatic' or 'atypical' myocarditis has also been documented in the literature with regards to clozapine use. In one study, six such cases were identified which presented with no symptoms, three of which were described as fatal (Ronaldson et al., 2010, 2011). Many of the patients were entirely asymptomatic and further, did not undergo the expected investigations that one might expect prior to their fatality. It is unclear to the authors whether these patients actually had myocarditis or not.

7.2. Cardiomyopathy

Cardiomyopathy is generally regarded as a chronic long-term disease and most often manifests months or years following exposure to causative agents. As with cardiomyopathy of any other cause, clozapine-induced cardiomyopathy presents with increasing breathlessness most commonly, alongside orthopnoea (inability to lie flat), paroxysmal nocturnal dyspnoea (waking up in the night gasping for breath and needing to sit up) and increasing peripheral oedema (Alawami et al., 2014). Common signs can include peripheral oedema, decreased exercise tolerance and evidence of central congestion (raised jugular venous pressure, coarse crackles at lung bases). In addition, systolic murmurs are common from possible mitral and/or tricuspid insufficiency. Drug-induced cardiomyopathy is rarely asymptomatic throughout its course, though in young and otherwise healthy individuals it can often present late at a stage with extremely poor LV systolic function. Malignant arrhythmia (ventricular tachycardia/fibrillation) and so-called 'pump failure' are established modes of death for all causes of cardiomyopathy.

7.3. Sinus tachycardia

In isolation, sinus tachycardia is not regarded as evidence of cardiotoxicity as it is a common feature of clozapine use and is largely benign (Merrill et al., 2005). However, it is mentioned here in part as it is very common, and can sometimes indicate underlying cardiotoxicity. Presence of a new sinus tachycardia should prompt examination of the patient and consideration of further investigations as below.

8. Diagnostic criteria

There are no clear diagnostic criteria for clozapine-induced cardiotoxicity. Some authors have proposed guidance although these are not in line with current cardiac practice, such that there is a significant risk of both under- and over-diagnosing patients. Given that clozapine-induced cardiotoxicity manifests and is treated in the same way as any other cause of myocarditis or cardiomyopathy (namely consideration of dose reduction and cessation of the causative agent), it is the authors' opinion that it should be investigated and diagnosed in this same manner, given the large evidence base underpinning this guidance.

The diagnostic criteria for myocarditis requires both clinical symptoms (chest pain, new breathlessness, palpitations, syncope, cardiogenic shock or sudden cardiac death) and one or more diagnostic criteria (electrocardiogram (ECG), biochemical or imaging changes) (Richardson et al., 1996). Goodison et al. found that 65% of patients labelled as having clozapine-induced myocarditis in the literature, did not fulfil the European Society of Cardiology criteria for myocarditis (Goodison et al., 2015). This has significant implications when discussing the incidence/outcomes of clozapine-induced myocarditis.

Some authors have made a diagnosis of clozapine-induced myocarditis through clinical and biochemical suspicion alone, with some patients having clozapine discontinued without myocardial imaging or endomyocardial biopsy (EMB) (Baptista et al., 2015; Chow et al., 2014; Munshi et al., 2014). This is unfortunate. As with most diseases, multiple investigative measures can support a diagnosis of clozapine-induced cardiotoxicity, such that the authors consider cardiac imaging as mandatory.

8.1. Myocarditis

1 ECG: The sensitivity and specificity for diagnosing myocarditis is low (Cooper, 2009); it is not recommended. ECG can be entirely normal or show sinus tachycardia or indeed any number of abnormalities. It is not uncommon for young patients presenting acutely to have ECG changes resembling acute myocardial infarction (Fig. 1) and subsequently undergoing invasive coronary angiography as a result (which is normal). Cardiac protocols therefore do not recommend the use of ECG in diagnosing myocarditis (Ronaldson et al., 2011) but it should remain a routine part of the work-up.

2 Biomarkers: Cardiac-specific biomarkers, namely troponin, are frequently used to investigate cardiac complaints. Troponin is a protein found in cardiac muscle, and in skeletal muscle to a lesser extent. It is an established marker of cardiac damage; high sensitivity troponins are guideline-based measurements for the identification of coronary ischaemia and inflammation. Myocarditis would be expected to be associated with very high troponin levels. When elevated in a young patient with new symptoms of chest pain and/or breathlessness, myocarditis should always be considered and this should trigger further investigation with cardiac imaging.

Many non-specific biomarkers have been linked to clozapine-induced myocarditis, including c-reactive protein (CRP). Ronaldson et al. found CRP levels increased prior to troponin in 90% of cases and on the basis of this, suggested that troponin and CRP be used routinely as early markers of clozapine-induced cardiotoxicity (Ronaldson et al., 2011). With the advent of high-sensitivity troponin, it is unclear how relevant CRP may remain. Beyond the clozapine cohorts, CRP is not used in the diagnosis of myocarditis.

Creatine kinase (CK) is another protein found in both skeletal and cardiac muscle and was previously used as a biomarker to diagnose myocardial injury, especially in myocardial infarction. However, troponin is significantly more sensitive and as such, CK is now rarely used. CK remains unhelpful in screening for myocarditis given its poor predictive value and should not be used routinely (Magnani and Dec, 2006).

3 Imaging: Transthoracic echocardiography (TTE) remains the most commonly used modality in the diagnosis of clozapine-induced myocarditis, as it does with all myocarditis (Albouaini et al., 2013). Findings normally show regional or global LV, or biventricular systolic dysfunction with normal wall thickness.

Similar findings are seen on cardiac magnetic resonance imaging (CMRI), though this modality provides superior information to TTE as it facilitates scar and oedema (inflammation) imaging within the myocardial tissues (Bellissima et al., 2018; Belloni et al., 2007; Chow et al., 2014) (Fig. 2). CMRI is regarded as being highly sensitive and specific in diagnosing acute myocarditis, providing information over and above that gained from TTE imaging, and should

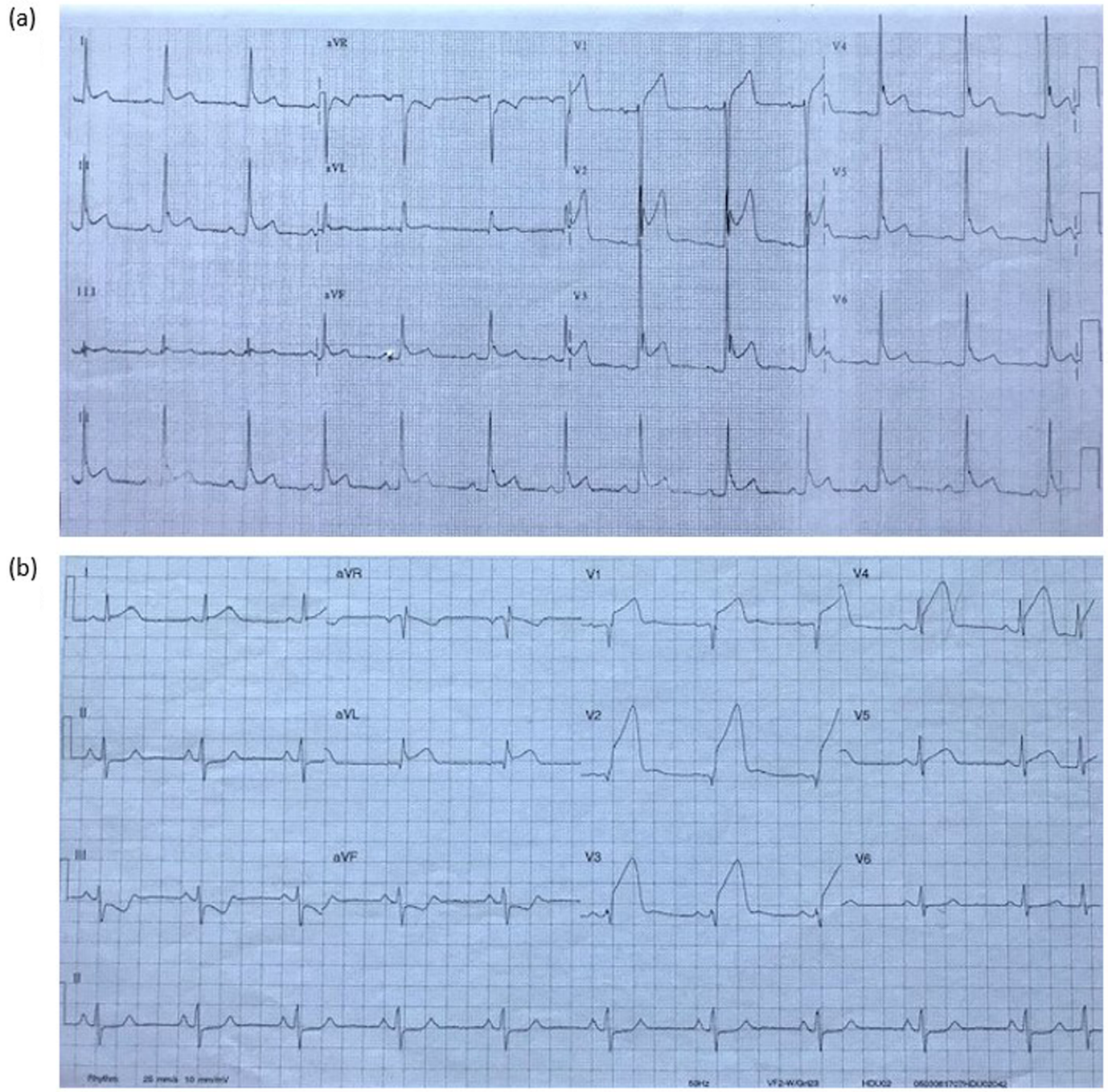

Fig. 1. 12-lead ECGs highlighting the similarity between acute myocarditis and acute myocardial infarction. ECG (a) represents an acute myocarditis with global saddle-shaped ST elevation in the majority of the 12 leads. ECG (b) represents an acute myocardial infarction with anterior ST elevation but demonstrates ST depression (reciprocal changes) in the 2 of the 3 inferior leads (Leads III and aVF).

always be performed alongside TTE in suspected cases where available (Friedrich et al., 2009). CMRI is now routinely undertaken in most centres but there is a cost implication to its routine use as compared to TTE and as such, its use is often reserved for cases where troponin levels and symptoms are suggestive of myocarditis, even in cases of normal TTE.

4 Biopsy: Endomyocardial biopsy (EMB) is the gold standard diagnostic tool for myocarditis (Pieroni et al., 2004). Despite this, it is undertaken rarely as imaging tests have evolved considerably and this invasive procedure does carry uncommon but significant risks (Wei et al., 2017). Its use is limited to cases of fulminant myocarditis when other causes of myocarditis need to be excluded (such as Giant Cell) which are invariably fatal without specific immunotherapy.

8.2. Cardiomyopathy

1 ECG: This does not form part of the diagnostic criteria for cardiomyopathy, but can provide valuable information both in terms of aetiology (Q waves seen in myocardial infarction, left ventricular hypertrophy and strain seen in hypertension etc.) and potential therapy (QRS duration when considering implantation of cardiac resynchronisation therapy devices).

2 Biomarkers: Brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) are hormones that are

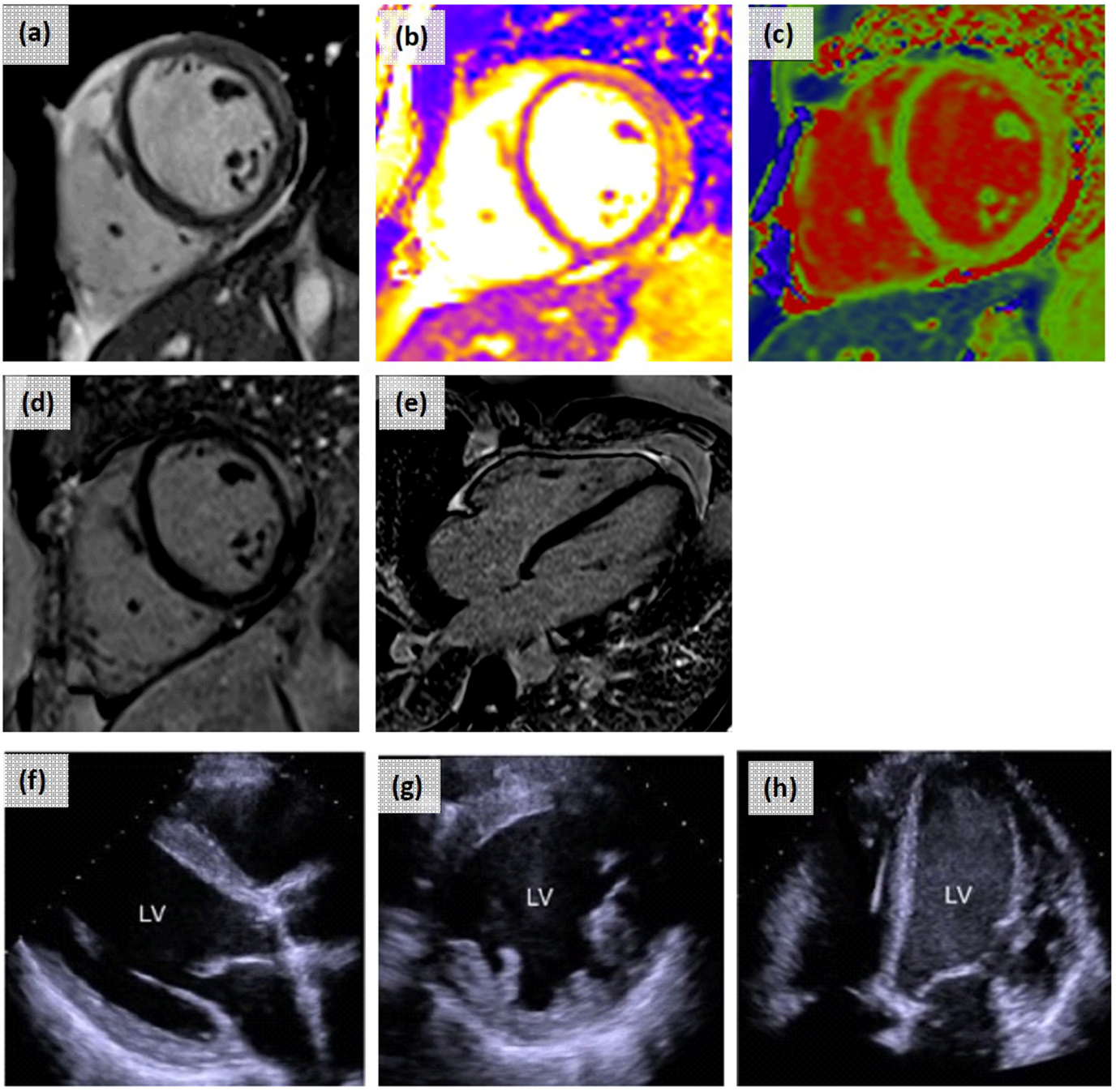

Fig. 2. Cardiac imaging in myocarditis and cardiomyopathy.Cardiac Magnetic Resonance Imaging (CMRI) demonstrating myocarditis. Cine imaging following gadolinium contrast (a) shows high signal in the lateral wall corresponding to high T2 values (b) T1 values (c) and patchy subepicardial late gadolinium enhancement seen in short-axis (d) and long-axis (e) views. Transthoracic Echocardiogram (TTE) demonstrating a dilated left ventricle in the parasternal long axis (f), parasternal short axis (g) and apical 4 chamber windows, which demonstrates evidence of spontaneous echo contrast in the left ventricle, a characteristic feature of left, ventricular impairment (h).

produced by the ventricles when the heart is subject to stretch (normally by increased volumes). These hormones are very beneficial in that they promote natriuresis and diuresis as well as a reduction in fibrosis and hypertrophy. Normal levels essentially rule out heart failure and cardiomyopathy and as such they are also guideline-based blood tests for access to specialist care when elevated. Both active myocarditis and cardiomyopathy can be associated with raised natriuretic peptide levels. Their role in clozapine-induced cardiomyopathy have not been sufficiently examined, but the authors would expect this to be very similar to all other causes of heart failure. As such, in any suspected case of cardiomyopathy, natriuretic peptide testing should always be undertaken. If elevated, further imaging tests are mandatory.

3 Imaging: TTE is the first imaging test that should be undertaken. Features include a dilated and thin-walled LV with systolic impairment (Fig. 2). CMRI imaging can provide additional information over TTE to further distinguish between other common causes of cardiomyopathy and can help aid prognostication. Given the rare occurrence of clozapine-induced cardiomyopathy, presence of specific features that distinguish it from other aetiologies of cardiomyopathy are currently lacking.

4 Biopsy: This is not routinely undertaken.

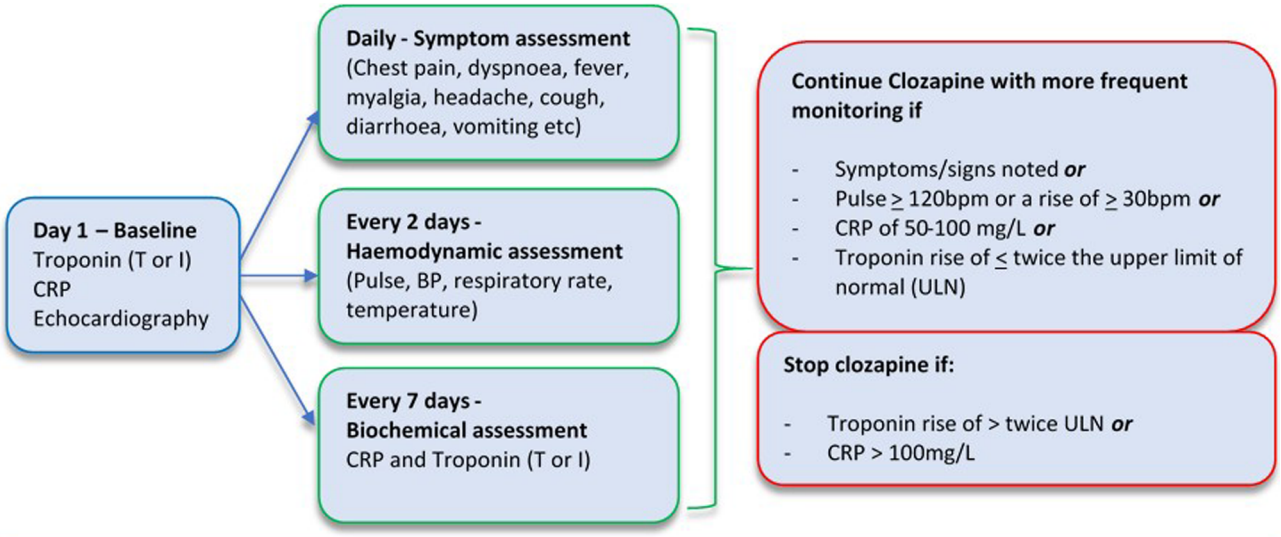

Fig. 3. Monitoring for signs of Clozapine-induced cardiotoxicity upon initiation of treatment.

Table 2
The starting and target doses of commonly used prognostic medications for left ventricular systolic impairment (ACE inhibitors, beta-blockers and mineralocorticoid receptor antagonists). Frequency can be once daily (OD), twice daily (BD) or three times per day (TDS).

Drug class and examples	Starting dose	Target dose
ACE inhibitors		
Ramipril	2.5 mg OD	10 mg OD
Lisinopril	2.5–5 mg OD	20 mg–35 mg OD
Enalapril	2.5 mg BD	10–20 mg BD
Captopril	6.25 mg TDS	50 mg TDS
Beta-blockers		
Bisoprolol	1.25 mg OD	10 mg OD
Carvedilol	3.125 mg BD	25 mg BD
Metoprolol tartrate	12.5–25 mg OD	200 mg OD
Mineralocorticoid receptor antagonists		
Spironolactone	25 mg OD	50 mg OD
Eplerenone	25 mg OD	50 mg OD

9. Monitoring

Only one protocol for monitoring of clozapine-induced cardiotoxicity exists, developed by Ronaldson et al. They recommend baseline troponin, CRP and TTE with assessment of biomarkers weekly, vital signs every other day and symptoms of illness daily (Fig. 3) (Ronaldson et al., 2011). The group advocate more frequent monitoring be performed if abnormalities in vital signs or biomarkers are detected (Ronaldson et al., 2011). If the troponin does not elevate to twice the upper limit of normal (2x ULN) or CRP levels do not rise above 100 mg/L, the advice is to continue clozapine (Ronaldson et al., 2011). If there is any suggestion that either CRP or troponin rise above the stated thresholds, then cardiology opinion should be sought, with a view to repeat imaging and cessation of clozapine (Ronaldson et al., 2011). The authors advocate caution in strict adherence to this guideline and feel that applying this protocol will improve safety of clozapine initiation without adding greatly to treatment costs.

Within cardiology there exists one other frequent cause of acute drug-induced cardiotoxicity. Trastuzamab is a life-prolonging breast cancer drug that is associated with a high incidence of cardiotoxicity during therapy. It is similar in importance in breast cancer as clozapine is for TRS, but is much more commonly available and as such, has had a great deal of interest. Dedicated cardiology clinics for those patients who have/are receiving Trastuzamab are increasingly common, with the aim of early guideline-based referral for cardiology advice with the specific view of improving cardiac function to facilitate ongoing use of this life-saving therapy.

It is the authors opinion that cessation of clozapine, whilst sometimes necessary, is not always mandatory. Cohesive investigations are necessary that should trigger cardiology review and these should be based on biomarker testing as clinically indicated. There are well-established medical therapies for LV systolic dysfunction of any cause (myocarditis or cardiomyopathy; see below) that can significantly improve cardiac function and may facilitate continued therapy with clozapine.

10. Therapy

The mainstay of therapy of clozapine-induced cardiotoxicity is *consideration* of clozapine cessation, specialist review and instigation of disease modifying cardiac treatment. In all cases of fulminant myocarditis or cases where there is new, at least moderate, LV dysfunction, clozapine should be withheld.

In any case of LV systolic dysfunction, disease modifying heart failure medications should be commenced under specialist supervision (Table 2) (Ponikowski et al., 2016). These drugs significantly improve morbidity and mortality and can facilitate myocardial recovery: Angiotensin-converting enzyme inhibitors (ACEi) together with beta-blockers are first line agents. If there is severe LV impairment, then a mineralocorticoid receptor antagonist (MRA) can also be added.

In the cohort of patients with trastuzamab-related LV systolic dysfunction, early instigation of the above medications very often facilitates ongoing anti-cancer therapy without further cardiac compromise.

Bisoprolol and carvedilol are cardio-selective beta-blockers. The potential hallucinogenic side effects of beta-blockers are rare with these formulations (Cruickshank, 2010), an important consideration for patients with established psychiatric disease.

The routine use of corticosteroids in the treatment of clozapine-induced myocarditis is not recommended. In wider clinical practice, the use of steroids is limited to rare, very fulminant specific conditions where EMB will be mandated to exclude an infectious cause.

11. Outcomes of clozapine cessation

The literature suggests that once the drug is discontinued, myocarditis usually resolves symptomatically and biochemically (Annamraju et al., 2007). Evidence is lacking for cardiomyopathy, but one case report suggests partial reversibility upon cessation of clozapine (de Knijff et al., 2001). There is evidence that cessation of clozapine

when LVEF is >40% has the best chance of complete recovery (Malik et al., 2015); the lower the LVEF, the worse the prognosis tends to be. The key therefore is in correctly identifying cardiotoxicity and involving specialist input sooner rather than later. None of the reviewed literature documented outcomes in those treated for the reduction of LV systolic function.

12. Re-introduction of clozapine in those with cardiotoxicity

In the event of LV recovery, reintroduction of clozapine is an important consideration (Manu et al., 2012). The significant majority of evidence however, relates to single case reports.

The success rate of clozapine "re-challenge" following myocarditis in one series was 50–70% (Nguyen et al., 2017; Ronaldson et al., 2012b). In these cases, clozapine re-introduction primarily occurred after many months off therapy with only 2 cases being within 11 days (Ronaldson et al., 2012b). From a cardiac perspective, this perhaps infers that the original myocardial insult either did not relate to clozapine or was mis-diagnosed.

Factors such as slower up-titration, close monitoring and longer period of time to re-challenge from discontinuation, have been suggested to help resume successful clozapine therapy (Rosenfeld et al., 2010). Evidence for clozapine re-challenge in cardiomyopathy is lacking. Notwithstanding, clozapine re-challenge can still result in cardiotoxicity and the need for further study in these patients remains relevant.

Fig. 4 illustrates the recommendations made by Cook et al. for monitoring during clozapine re-challenge. They suggest baseline biomarkers and TTE on day 1 of clozapine re-challenge, followed by serial TTE and repeat biomarker measurements taken at several time intervals throughout the up-titration of clozapine (Cook et al., 2015). Given the absence of evidence-based guidance in the literature, this strategy offers a systematic approach for monitoring during re-challenge.

ACEi could also be used to aid re-challenge, and even facilitate continued use of clozapine; a strategy already adopted in patients needing Trastuzamab for breast cancer therapy (Fanous and Dillon, 2016; Hamirani et al., 2016). Abdel-Wahab found that the ACEi captopril had a cardio-protective effect against clozapine-induced myocarditis in rats (Abdel-Wahab et al., 2014). Rostagno also suggested that the use of beta-blockers and ACEi may allow resumption of clozapine after withdrawal for cardiotoxicity (Rostagno et al., 2008). This is an area with little research with regards to clozapine that may allow for the continuation of effective, safe therapy.

13. Pre-existing heart conditions

Most of the literature focuses on clozapine-induced cardiotoxicity in those with preceding normal cardiac structure and function. Current guidelines and evidence do not focus on patients with established heart disease, such that most evidence is in the form of case reports.

Sanchez et al. highlights the case of a 36-year-old with hypertrophic cardiomyopathy requiring clozapine for TRS (Sanchez et al., 2016). The guidance on clozapine initiation and monitoring was followed and despite an asymptomatic yet significant rise in troponin levels, it was safely continued with cardiology advice (Sanchez et al., 2016). This report highlights the need for early specialist input and the ability to continue clozapine safely despite apparently abnormal blood results.

The authors feel that specialist cardiology review would provide guidance as to the safety of starting clozapine. With regular cardiology input and appropriate disease modifying therapy, many of those labelled as having pre-existing cardiac conditions might safely receive clozapine.

14. Discussion

Clozapine is a very effective medication for TRS; however, it is markedly underused in clinical practice. Clozapine-induced cardiotoxicity is likely over-reported in the literature, with few patients receiving diagnostic cardiac imaging or myocardial biopsy. It is possible that this condition is rarer than thought and further, that many patients have therapy discontinued unnecessarily. Lastly, BNF guidance advocates caution in using clozapine in those with prior cardiac complaints, resulting in many patients receiving advice to not initiate or discontinue clozapine when this may not be the case.

The challenge amongst clinicians and patients alike remains noteworthy, especially considering the importance of baseline and regular blood test monitoring to screen for cardiotoxicity in these patients. 56–65% of clinicians in one survey identified patient refusal of obtaining baseline blood tests and regular blood monitoring as the major barriers to initiating treatment with clozapine (Gee et al., 2014). Another survey of 50 patients found that only 30% would take clozapine, with 49% citing hospital admission as the biggest issue for treatment initiation (Gee et al., 2017) – this is rarely needed for cardiac monitoring however.

As stated, there are significant concerns with regards to the accuracy of diagnosis of cardiotoxicity. A significant proportion of patients may be being inaccurately labelled with cardiotoxicity and this stems from a clear lack of established guidelines for diagnosis. This extends to the limited guidance for monitoring patients being initiated on clozapine therapy or for those being restarted on treatment following cessation of the drug. This must be a clear focus for further work to ensure patients are both accurately diagnosed and therefore managed accordingly.

As stated earlier, the use of disease modifying heart failure medications to facilitate ongoing chemotherapy in chemotherapy-induced cardiotoxicity highlights another key area for research in this field. More evidence is needed as to whether these same agents, used in all cases of heart failure regardless of cause, can help improve cardiac function in patients with clozapine-induced cardiotoxicity such that this drug might be tolerated. This could allow a significant number of patients to not only be treated safely for cardiotoxicity but continue their clozapine alongside cardiac treatments – this would no doubt offer morbidity and mortality benefits from both psychiatric and cardiovascular perspectives.

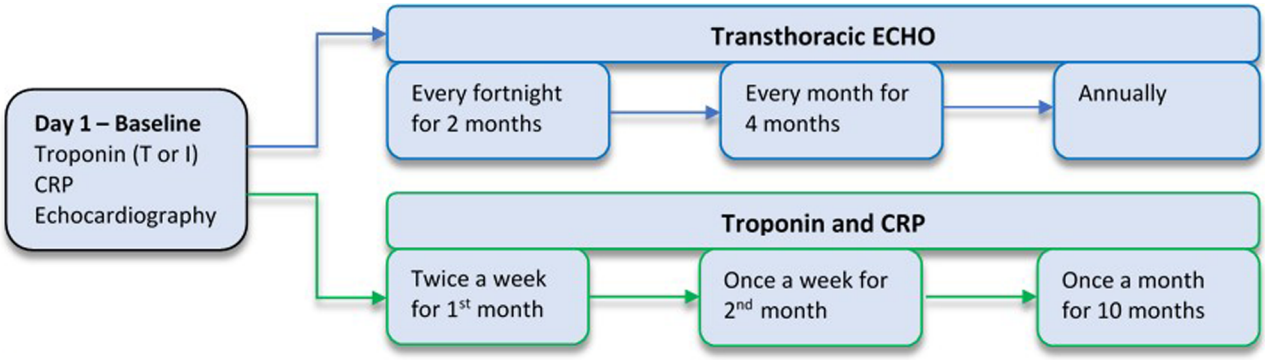

Fig. 4. Recommendations for monitoring during re-challenge.

Effective therapeutic managements exist for stabilisation and improvement in LV function in either myocarditis or cardiomyopathy. The authors advocate for early cardiology input and feel that with adequate support, increased clozapine use can be safely facilitated.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112491.

References

Abdel-Wahab, B.A., Metwally, M.E., 2014. Clozapine-induced cardiotoxicity in rats: involvement of tumour necrosis factor alpha, NF-κβ and caspase-3. Toxicol. Rep. 1, 1213–1223.

Abdel-Wahab, B.A., Metwally, M.E., 2015. Clozapine-induced cardiotoxicity: role of oxidative stress, tumour necrosis factor alpha and NF-κβ Cardiovasc. Toxicol. 15, 355–365.

Abdel-Wahab, B.A., Metwally, M.E., El-khawanki, M.M., Hashim, A.M., 2014. Protective effect of captopril against clozapine-induced myocarditis in rats: role of oxidative stress, proinflammatory cytokines and DNA damage. Chem. Biol. Interact. 216, 43–52.

Alawami, M., Wasywich, C., Cicovic, A., Kenedi, C., 2014. A systematic review of clozapine induced cardiomyopathy. Int. J. Cardiol. 176, 315–320.

Albouaini, K., Ruzsics, B., Chenzbraun, A., 2013. Multimodality cardiac imaging in clozapine-induced eosinophilic constrictive perimyocarditis. Eur. Heart J. Cardiovasc. Imaging 14, 338.

Annamraju, S., Sheitman, B., Saik, S., Stephenson, A., 2007. Early recognition of clozapine-induced myocarditis. J. Clin. Psychopharmacol. 27, 479–483.

Baptista, T., Rojas, N., Dávila, D.F., 2015. Heterogeneity of clozapine-associated myocarditis: an opportunity for novel preventing strategies. Aust. N. Z. J. Psychiatry 49, 1068.

Bellissima, B.L., Tingle, M.D., Cicović, A., Alawami, M., Kenedi, C., 2018. A systematic review of clozapine-induced myocarditis. Int. J. Cardiol. 259, 122–129.

Belloni, E., De Cobelli, F., Esposito, A., Mellone, R., Gentinetta, F., Meloni, C., Del Maschio, A., 2007. Myocarditis associated with clozapine studied by cardiovascular magnetic resonance. J. Cardiovasc. Magn. Reson. Off. J. Soc. Cardiovasc. Magn. Reson. 9, 591–593.

Brown, S., Inskip, H., Barraclough, B., 2000. Causes of the excess mortality of schizophrenia. Br. J. Psychiatry J. Ment. Sci. 177, 212–217.

Chow, V., Feijo, I., Trieu, J., Starling, J., Kritharides, L., 2014. Successful rechallenge of clozapine therapy following previous clozapine-induced myocarditis confirmed on cardiac MRI. J. Child Adolesc. Psychopharmacol. 24, 99–101.

Cook, S.C., Ferguson, B.A., Cotes, R.O., Heinrich, T.W., Schwartz, A.C., 2015. Clozapine-induced myocarditis: prevention and considerations in rechallenge. Psychosomatics 56, 685–690.

Cooper, L.T., 2009. Myocarditis. N. Engl. J. Med. 360, 1526–1538.

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., et al., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 16, 163–180.

Cruickshank, J.M., 2010. Beta-blockers and heart failure. Indian Heart J. 62, 101–110.

De Berardis, D., Serroni, N., Campanella, D., Olivieri, L., Ferri, F., Carano, A., Cavuto, M., Martinotti, G., Cicconetti, A., Piersanti, M., et al., 2012. Update on the adverse effects of clozapine: focus on myocarditis. Curr. Drug Saf. 7, 55–62.

De Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.-J., Ndetei, D.M., et al., 2011. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 10, 52–77.

Dunlop, J., Brandon, N.J., 2015. Schizophrenia drug discovery and development in an evolving era: are new drug targets fulfilling expectations? J. Psychopharmacol. Oxf. Engl. 29, 230–238.

Fanous, I., Dillon, P., 2016. Cancer treatment-related cardiac toxicity: prevention, assessment and management. Med. Oncol. Northwood Lond. Engl. 33, 84.

Fitton, A., Benfield, P., 1993. Clozapine: an appraisal of its pharmacoeconomic benefits in the treatment of schizophrenia. Pharmacoeconomics 4, 131–156.

Friedrich, M.G., Sechtem, U., Schulz-Menger, J., Holmvang, G., Alakija, P., Cooper, L.T., White, J.A., Abdel-Aty, H., Gutberlet, M., Prasad, S., et al., 2009. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J. Am. Coll. Cardiol. 53, 1475.

Gee, S., Vergunst, F., Howes, O., Taylor, D., 2014. Practitioner attitudes to clozapine initiation. Acta Psychiatr. Scand. 130, 16–24.

Gee, S.H., Shergill, S.S., Taylor, D.M., 2017. Patient attitudes to clozapine initiation. Int. Clin. Psychopharmacol. 32, 337–342.

Goodison, G., Siskind, D., Harcourt-Rigg, C., Hipgrave, W., Burrage, M., Kiff, S., Wallace, M., 2015. Clarifying the diagnosis of myocarditis in a patient on clozapine. Australas. Psychiatry Bull. R. Aust. N. Z. Coll. Psychiatr. 23, 311–313.

Hamirani, Y., Fanous, I., Kramer, C.M., Wong, A., Salerno, M., Dillon, P., 2016. Anthracycline- and trastuzumab-induced cardiotoxicity: a retrospective study. Med. Oncol. Northwood Lond. Engl. 33, 82.

Hill, G.R., Harrison-Woolrych, M., 2008. Clozapine and myocarditis: a case series from the New Zealand Intensive Medicines Monitoring Programme. N. Z. Med. J. 121, 68–75.

Kilian, J.G., Kerr, K., Lawrence, C., Celermajer, D.S., 1999. Myocarditis and cardiomyopathy associated with clozapine. Lancet Lond. Engl. 354, 1841–1845.

Kluge, M., Schuld, A., Schacht, A., Himmerich, H., Dalal, M.A., Wehmeier, P.M., Hinze-Selch, D., Kraus, T., Dittmann, R.W., Pollmächer, T., 2009. Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. Psychoneuroendocrinology 34, 118–128.

de Knijff, D.W., Schepers, P.H., Blanken-Meijs, J.T., 2001. Cardiomyopathy during clozapine therapy. Ned. Tijdschr. Geneeskd. 145, 1697–1699.

Layland, J.J., Liew, D., Prior, D.L., 2009. Clozapine-induced cardiotoxicity: a clinical update. Med. J. Aust. 190, 190–192.

Longhi, S., Heres, S., 2017. Clozapine-induced, dilated cardiomyopathy: a case report. BMC Res. Notes 10, 338.

Magnani, J.W., Dec, G.W., 2006. Myocarditis: current trends in diagnosis and treatment. Circulation 113, 876–890.

Malik, S.A., Malik, S., Dowsley, T.F., Singh, B., 2015. Left ventricular thrombus as a complication of clozapine-induced cardiomyopathy: a case report and brief literature review. Case Rep. Cardiol. 2015, 835952.

Manu, P., Sarpal, D., Muir, O., Kane, J.M., Correll, C.U., 2012. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophr. Res. 134, 180–186.

Merrill, D.B., Dec, G.W., Goff, D.C., 2005. Adverse cardiac effects associated with clozapine. J. Clin. Psychopharmacol. 25, 32–41.

Munshi, T.A., Volochniouk, D., Hassan, T., Mazhar, N., 2014. Clozapine-induced myocarditis: is mandatory monitoring warranted for its early recognition? Case Rep. Psychiatry 2014, 513108.

Nguyen, B., Du, C., Bastiampillai, T., Dhillon, R., Tibrewal, P., 2017. Successful clozapine re-challenge following myocarditis. Australas. Psychiatry Bull. R. Aust. N. Z. Coll. Psychiatr. 25, 385–386.

Pieroni, M., Cavallaro, R., Chimenti, C., Smeraldi, E., Frustaci, A., 2004. Clozapine-induced hypersensitivity myocarditis. Chest 126, 1703–1705.

Pollmächer, T., Hinze-Selch, D., Mullington, J., 1996. Effects of clozapine on plasma cytokine and soluble cytokine receptor levels. J. Clin. Psychopharmacol. 16, 403–409.

Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., Falk, V., González-Juanatey, J.R., Harjola, V.-P., Jankowska, E.A., et al., 2016. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Rev. Espanola Cardiol. Engl. Ed. 69, 1167.

Razminia, M., Salem, Y., Devaki, S., Shah, N., Khosla, S., 2006. Clozapine induced myopericarditis: early recognition improves clinical outcome. Am. J. Ther. 13, 274–276.

Richardson, P., McKenna, W., Bristow, M., Maisch, B., Mautner, B., O'Connell, J., Olsen, E., Thiene, G., Goodwin, J., Gyarfas, I., et al., 1996. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 93, 841–842.

Ronaldson, K.J., Taylor, A.J., Fitzgerald, P.B., Topliss, D.J., Elsik, M., McNeil, J.J., 2010. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. J. Clin. Psychiatry 71, 976–981.

Ronaldson, K.J., Fitzgerald, P.B., Taylor, A.J., Topliss, D.J., McNeil, J.J., 2011. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust. N. Z. J. Psychiatry 45, 458–465.

Ronaldson, K.J., Fitzgerald, P.B., Taylor, A.J., Topliss, D.J., Wolfe, R., McNeil, J.J., 2012Aa. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. Schizophr. Res. 141, 173–178.

Ronaldson, K.J., Fitzgerald, P.B., Taylor, A.J., McNeil, J.J., 2012Ab. Observations from 8 cases of clozapine rechallenge after development of myocarditis. J. Clin. Psychiatry 73, 252–254.

Rosenfeld, A.J., Gibbs, T., Ivie, R., Clarke, L., Merrill, D.B., 2010. Successful clozapine retrial after suspected myocarditis. Am. J. Psychiatry 167, 350–351.

Rostagno, C., Di Norscia, G., Placidi, G.F., Gensini, G.F., 2008. Beta-blocker and angiotensin-converting enzyme inhibitor may limit certain cardiac adverse effects of clozapine. Gen. Hosp. Psychiatry 30, 280–283.

Sanchez, A.Y.A., Foster, J.J., Plymen, C.M., Shergill, S., 2016. Clozapine in a patient with treatment-resistant schizophrenia and hypertrophic cardiomyopathy: a case report. BJPsych Open 2, 390–393.

Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can. J. Psychiatry Rev. Can. Psychiatr. 62, 772–777.

Stroup, T.S., Gerhard, T., Crystal, S., Huang, C., Olfson, M., 2016. Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. Am. J. Psychiatry 173, 166–173.

Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., Haukka, J., 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet Lond. Engl. 374, 620–627.

Wang, J.-F., Min, J.-Y., Hampton, T.G., Amende, I., Yan, X., Malek, S., Abelmann, W.H., Green, A.I., Zeind, J., Morgan, J.P., 2008. Clozapine-induced myocarditis: role of catecholamines in a murine model. Eur. J. Pharmacol. 592, 123–127.

Warnez, S., Alessi-Severini, S., 2014. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry 14, 102.

Wei, S., Fu, J., Chen, L., Yu, S., 2017. Performance of cardiac magnetic resonance imaging for diagnosis of myocarditis compared with endomyocardial biopsy: a meta-analysis. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 23, 3687–3696.

Youssef, D.L., Narayanan, P., Gill, N., 2016. Incidence and risk factors for clozapine-induced myocarditis and cardiomyopathy at a regional mental health service in Australia. Australas. Psychiatry Bull. R. Aust. N. Z. Coll. Psychiatr 24, 176–180.