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Clozapine rechallenge following myocarditis: a systematic review of rechallenge cases

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Review

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Abstract

Introduction and Objectives. Clozapine is the antipsychotic medication with the greatest efficacy in treatment-resistant schizophrenia (TRS). Unfortunately, clozapine is ceased in approximately 0.2% to 8.5% of people due to concerns about clozapine-associated myocarditis (CAM). The opportunity for clozapine rechallenge is important for people with TRS and CAM, due to limited alternative treatments. However, there is a lack of consensus regarding the optimal process, monitoring, and dose titration to achieve successful clozapine rechallenge. The study aimed to review the process, monitoring, and dose titration within cases of clozapine rechallenge after CAM, to identify features associated with successful rechallenge.

Methods. A systematic review of clozapine rechallenge cases following CAM was conducted. PubMed, EMBASE, Cinahl, and PsycINFO were searched for cases. Reference lists of retrieved articles and field experts were consulted to identify additional studies.

Results. Forty-five cases were identified that described clozapine rechallenge, 31 of which were successful. Successful rechallenge cases generally used a slower dose titration regime with more frequent monitoring than standard clozapine initiation protocols; however, this data was not always completely recorded within cases. Six cases referred to published rechallenge protocols to guide their rechallenge.

Conclusions. The process, monitoring, and dose titration of clozapine rechallenge are inconsistently reported in the literature. Despite this, 69% of case reports detailed a successful rechallenge post CAM; noting limitations associated with reliance on case data. Ensuring published clozapine rechallenge cases report standardised data, including titration speed and monitoring frequencies, is required to guide the development and validation of guidelines for clozapine rechallenge.

Introduction

Schizophrenia is a mental disorder associated with significant lifelong disability,[1] and has a substantial impact on individuals, caregivers, and health services.[2] Approximately one-third of people do not respond to standard treatments and meet the criteria for treatment-resistant schizophrenia (TRS).[3,4] Clozapine is an atypical antipsychotic that has demonstrated superior efficacy for managing TRS.[5,6] However, clozapine's use is limited by its significant adverse effect burden[7], including weight gain and risk of metabolic syndrome[8], serious constipation,[9] postural hypotension,[10] sialorrhea,[11] nocturnal enuresis,[12] neutropenia,[13] and risk of myocarditis.[14].

Incidence of clozapine-associated myocarditis (CAM) has been reported at 0.2% and 8.5% worldwide, most commonly occurring in the first three to four weeks of treatment commencement.[14–16] Signs and symptoms of myocarditis are often non-specific, such as tachycardia, chest pain, dyspnoea, fever, eosinophilia, and malaise, and can be difficult to differentiate from other adverse effects.[17] If not detected early, CAM is associated with high morbidity and mortality.[17–19] Hence, weekly monitoring with serial C-reactive protein (CRP) and troponin levels is recommended for the first four weeks.[17] The pathophysiology of CAM is poorly understood; however, an IgE-mediated hypersensitivity reaction has been proposed, with serum eosinophilia and eosinophilic infiltrates on endomyocardial biopsy.[17,20,21] Clozapine has also been associated with pro-inflammatory cytokine and hyper-catecholaminergic states in animal models and may have a direct cardiotoxic effect.[21–23] Risk factors for CAM have been explored previously, with rapid

titration of clozapine, and concurrent prescription of sodium valproate being the strongest risks.[21,24,25]

Myocarditis is a significant complication and clinical practice suggests clozapine be withheld if CAM is suspected, which most often results in the resolution of myocarditis.[26,27] However, discontinuing clozapine may result in relapse of psychotic symptoms as well as discontinuation symptoms.[28,29] Due to strict monitoring protocols and nuanced discrepancies between guidelines, myocarditis may be overdiagnosed in some jurisdictions, asindividuals may have subclinical troponin leaks due to underlying cardiac conditions, viral illness, or illicit substance misuse. The gold standard for diagnosing CAM is cardiac biopsy or cardiac magnetic resonance imaging (CMR), which may not be feasible in some clinical settings. This detection bias may lead to unnecessary discontinuation.

Clozapine rechallenge in individuals with CAM is an important treatment consideration due to otherwise limited efficacious treatment alternatives in the setting of TRS. It is unclear from the current literature what rechallenge process, monitoring, and dose titration is the safest and most successful.[30] Previous systematic reviews have not focused exclusively on rechallenge cases post-CAM, including only brief descriptions of a subsection of their included studies that undertook rechallenge.[14,16,27,31,32] An updated review of the literature will set the scene for the development of much-needed standardised rechallenge protocols. The study aimed to review the process, monitoring, and dose titration within cases of clozapine rechallenge after CAM, to identify features associated with successful rechallenge.

Methods

Guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[33] were followed (PRISMA Checklist Appendix 8) and the protocol for this systematic review was registered with PROSPERO (CRD 42023418907). There were no changes to the protocol.

Search Strategy

The databases PubMed, EMBASE, Cinahl and PsychINFO were searched from inception to February 2024 using the search string "Clozapine AND Myocarditis." No language restrictions were applied. All records, abstracts, and full-text articles were screened independently by two different authors (LM, MG, CF) and when consensus was lacking, a senior author (DS, NK) was consulted. We consulted clozapine-associated-myocarditis experts about unpublished data and reviewed reference lists to identify additional cases. A search of preprint publications in both medRxiv and PsyArXiv Preprints was completed by two authors (DS, NW). We included all cases and case series that described people with a suspected or confirmed diagnosis of CAM who were subsequently rechallenged with clozapine. Studies that focused on CAM during initial clozapine exposure, or in clozapine re-trials other than following CAM (e.g. retrial following non-compliance), were excluded. Two unpublished case reports from the authors were included. Individuals provided informed consent for their deidentified information to be used in clinical publications.

Data extraction

Extracted case data included: demographics, duration of clozapine exposure before developing the index episode of CAM, clozapine dose at the time of clozapine cessation, time to rechallenge, involvement of cardiology services, pre-rechallenge cardiac screening, rechallenge monitoring criteria and frequency, and the rechallenge dosing strategy. Extraction was conducted independently by at least two authors (NK, LM, DS, NW).

The rechallenge was considered successful if the clozapine rechallenge had not been ceased due to the recurrence of CAM. If a case had multiple rechallenges, we only included data on the final rechallenge contributing to the outcome data and index episode of CAM being before the first retrial. Where possible, successful and unsuccessful cases were matched in our qualitative analysis. To facilitate comparison of titration rates across studies, this was represented as days to milestone clozapine doses.

We systematically assessed the quality of case reports and case series using the Joanna Briggs Institute (JBI) critical appraisal tools.[34,35] Each article was assessed for quality by two authors (LM, MG) (see Appendix 7).

Statistical analysis

Extracted data were summarised using descriptive statistics with SPSS.[36] Data was tested for normality using histograms and the Shapiro–Wilk test of normality.[37] Non-parametric data was reported using median and interquartile range (IQR), and compared using Mann-Whitney U tests for continuous data. Continuous parametric data was reported using mean and standard deviation (SD) and compared with independent T-tests. Dichotomous data was compared using the Fisher exact test due to the relatively small sample sizes. The outcome of the rechallenge was considered the independent variable. A p-value $\leq .05$ was considered statistically significant in comparing outcomes.

Results

Following database searches, a total of 1539 articles were retrieved, with 66 articles included for full-text screening. The reasons for exclusion at the full-text level are presented in Appendix 6 and the PRISMA flow chart (Figure 1). Case data was taken from 45 cases, which included the two unpublished case reports (see Appendix 1), a pre-print case report, and a case with two rechallenges for the same individual.

Pooled demographic data of the included studies is presented in Table 1 and Appendix 5. The mean age was 29 (SD 9; 95% CI, 26 to 32) years, 30 (67%) of 45 cases were male, and all patients had a diagnosis of schizophrenia or schizoaffective disorder. Clozapine treatment had been at a median dose of 225 (IQR 138) mg daily for a median time of 18 (IQR 5) days prior to individuals developing their index episode of CAM.

Critical appraisal

Generally, there was a high quality amongst the published cases, with a mean JBI score of 7.3/8. We found heterogeneity in the quality of the case series, with a mean score of 7.2/10. Of note, 3/5 case series lacked consecutive and complete inclusion of participants[30,38,39], and 2/5 provided a limited description of inclusion criteria.[30,39]

Outcomes of clozapine rechallenge

Following the rechallenge, 14 (31%) of 45 individuals re-developed CAM, and 31 (69%) successfully resumed clozapine. The median

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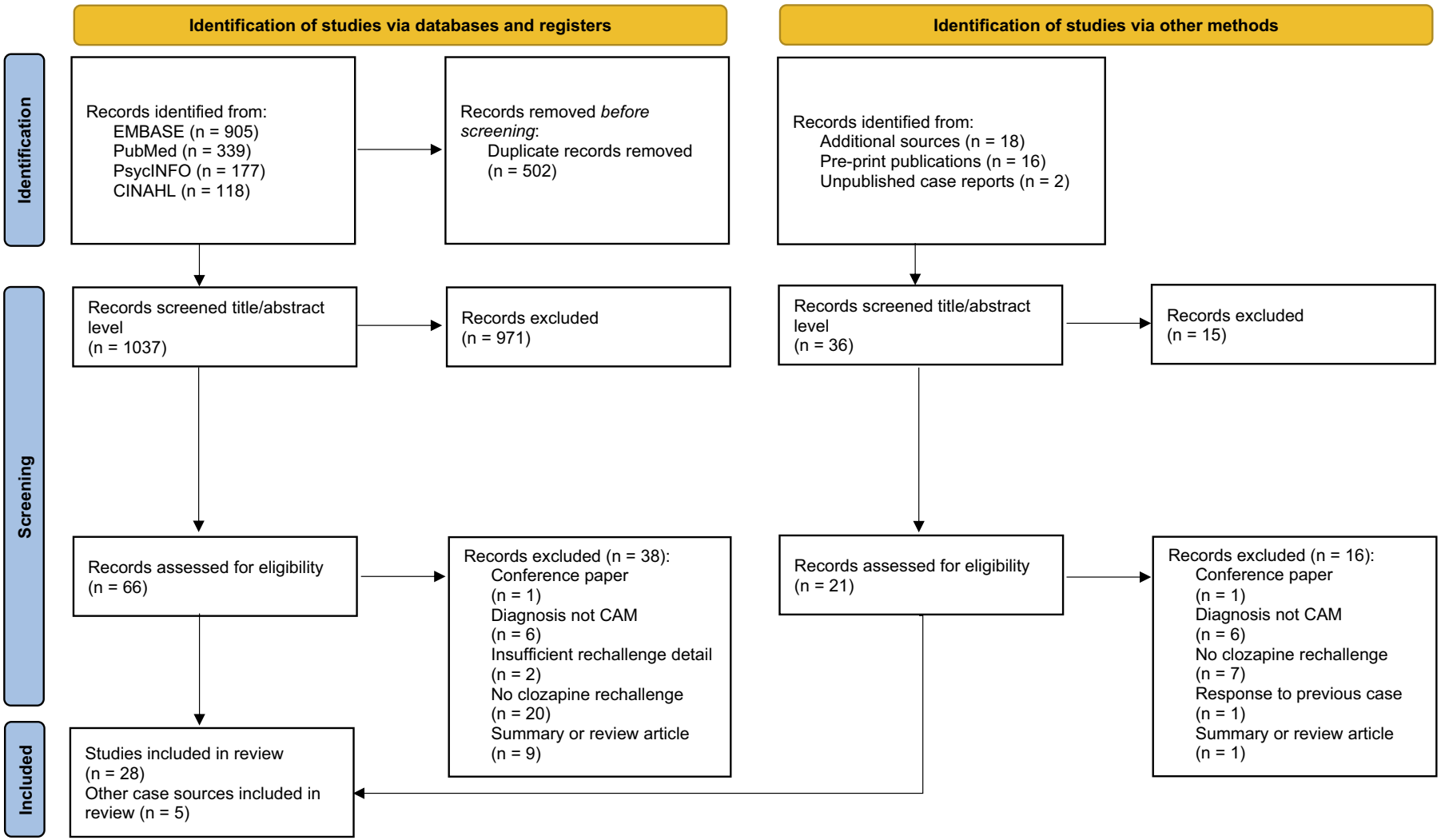

Figure 1. PRISMA flow diagram.

Table 1. Results

Variables present in rechallenge	Total	Unsuccessful cases	Successful cases	p-value
Male sex n(%)	30(66.67)	8(26.67)	22(73.33)	.238
Female sex n(%)	4(8.89)	0	4(100)	.552
Age (years)	28.65(8.54)	31.63(11.54)	27.61(7.27)	.259
Use of prophylactic cardiac medications n(%)	5(11.11)	1(20)	4(80)	.57
Engagement with cardiology prior to rechallenge n(%)	22(48.89)	4(18.18)	18(81.82)	.07
Time before clozapine rechallenge (months)[a]	6(7.96)	4(7.17)	7.5(13.7)	.17
Baseline TTE present n(%)	15(33.33%)	0	15(100)	.001
Baseline ECG present n(%)	11(24.44%)	0	11(100)	.0066
Serial TTE monitoring present n(%)	12(26.67%)	1(8.33)	11(91.67)	.047
Serial ECG monitoring present n(%)	13(28.89%)	1(7.69)	12(92.31)	.031
Clozapine level monitoring present n(%)	5(11.11%)	1(20)	4(80)	.569
CRP monitoring present n(%)	28(62.22%)	7(25)	21(75)	.256
Troponin monitoring present n(%)	30(66.67%)	7(23.33)	23(76.67)	.111
Starting rechallenge dose (mg)[a]	12.5(4.69)	12.5(46.88)	12.5(6.25)	.129
Time to reach ≥50 mg in rechallenge (days)[a]	9(19)	3(4)	18.5(20)	.002
Time to reach ≥100 mg in rechallenge (days)[a]	35(55)	1(IQR U/R)	49(62)	U/R
Time to reach ≥300 mg in rechallenge (days)[a]	73.5(158)	6(IQR U/R)	115.5(165)	U/R

U/R – unable to be reported
[a]Denotes non-parametric data

time elapsed before undertaking rechallenge was eight (IQR 14) months in successful cases, compared to four (IQR 7) months in unsuccessful cases (p = .17).

In unsuccessful cases, suspected CAM was detected at a median of six (IQR 5) days and a median clozapine dose of 50 (IQR 122) mg daily. The majority (88%) of cases developed CAM sooner in the rechallenge than their respective index episodes (p = .001). No unsuccessful rechallenge case was fatal. For individuals who underwent unsuccessful rechallenge, there were no reported persisting cardiac morbidity, although this may not have been rigorously assessed and documented.

Rechallenge clozapine dosing

The median starting dose across all rechallenge cases was 12.5 (IQR 5) mg daily. Eight cases started lower than 12.5 mg and six cases started at clozapine doses higher than 12.5 mg. When reported, starting doses in rechallenge were all equal to or lower than individuals' respective initial clozapine trials. Speed of dose up-titration was variably reported across cases. To reach a 50 mg daily dose, successful cases took a median of 18.5 (IQR 20) days, and unsuccessful cases 3 (IQR 4) days (p = .002). The mean final clozapine dose in successful cases was 366.7 (SD 182; 95% CI, 276 to 457) mg daily, which was achieved after a mean of 26 (SD 18; 95% CI, 15 to 37) weeks. Tachycardia was reported to slow the dose titration in one case,[40] and aberrant pathology results in two cases.[26,41]

Rechallenge preparation

In 31 (69%) of 45 cases, a collaborative risk assessment discussion was clearly documented. This frequently involved cardiology input (22/45 cases, 49%), which did not differ between cases later identified as successful or unsuccessful (see Table 1). Prophylactic use of cardiac medications, such as angiotensin-converting-enzyme inhibitors (ACEi) or beta-blockers (BB), was reported in five cases and there was no difference in rechallenge success in those taking cardiac medications. Two successful cases specified ceasing sodium valproate prior to rechallenge.[42,43]

Clinical monitoring

Rechallenge setting was reported in 16 of 45 cases , of which, two successful cases and one unsuccessful case were conducted as outpatients, with the remainder (13/16) of cases utilised an inpatient setting. Physical observations, such as blood pressure, temperature, heart rate, and oxygen saturation were documented as monitored in 20 (44%) of 45 cases. The frequency and duration of the monitoring regime were variable between cases, with more frequent monitoring in the first two to four weeks. Specific monitoring of features suggestive of myocarditis (e.g. flu-like symptoms, chest pain, dyspnoea, malaise, etc.) was documented to occur in eight (18%) of 45 rechallenge cases. Baseline ECG was reported in 11 (24%) of 45, with more successful cases undertaking ECG at baseline than unsuccessful cases. Serial ECG monitoring was conducted in 13 (29%) cases, with the frequency of testing ranging from daily to weekly. More successful cases (12/31) than unsuccessful cases (1/14) recorded regular ECG monitoring throughout rechallenge.

Pathology

Baseline blood investigations were reported in 16 (36%) cases, with three cases specifically detailing the need for improving biomarker trends prior to clozapine rechallenge.[44–46] CRP and troponin were the most frequently measured biomarkers at baseline and during monitoring. These two parameters were reported in rechallenge monitoring more commonly in successful than unsuccessful cases. CRP monitoring was reported in 27 (60%) of 45 during rechallenge, with a frequency specified in 20 cases: daily (8/27); second daily

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(1/27); twice weekly (5/27); three times weekly (1/27); and weekly (5/27). Troponin monitoring was reported in 29 (64%) cases during their rechallenge. The reported frequency of troponin monitoring ranged from daily to once weekly, with daily troponin most commonly measured (7/20 cases), followed by twice weekly monitoring (5/20). Some studies specified testing for monocytes or eosinophils, however, others recognised these are part of a full blood count (FBC) panel required for routine monitoring for clozapine-associated neutropenia (see Appendix 3). Tests such as B-type natriuretic peptide (BNP) and creatine kinase (CK) were less frequently used in serial monitoring (three and two cases respectively), with a greater level of testing for these markers at baseline (five and four cases respectively). Monitoring of clozapine levels was documented in five cases; weekly in one case, monthly in two cases, and a timeframe not specified in two cases. One case that monitored for clozapine levels was unsuccessful and the other four were successful.

Imaging

Baseline transthoracic echocardiography (TTE) was obtained in 15 (33%) of 45 cases prior to rechallenge (Table 1). Serial TTE was undertaken in nine cases (either weekly or monthly), with an additional three cases undertaking a solitary TTE as part of monitoring. Successful cases more frequently recorded TTE at baseline and as part of ongoing rechallenge monitoring than unsuccessful cases. CMR was conducted at baseline in four (9%) of 45 cases,[41,47–49] with one case arranging follow-up monitoring with CMR at 21 weeks,[49] and four cases utilising CMR for diagnostic proposes if individuals became symptomatic during the rechallenge.[30,41,46]

Discussion

Successful clozapine rechallenge following CAM occurred in over two-thirds of the 45 cases, with no significant morbidity or mortality associated with unsuccessful cases. Although there was no difference in starting clozapine dose, successful rechallenge cases employed slower clozapine up-titration and utilised TTE (weekly to monthly frequencies reported in the cases) and ECG (daily to weekly frequencies reported in the cases) monitoring more frequently than unsuccessful rechallenge cases. Daily CRP and troponin levels were the most frequent forms of pathology monitoring detailed in the cases and were more commonly reported in successful cases. Of note, repeated CAM on rechallenge occurred earlier and at a lower dose of clozapine compared with initial CAM.

This study adds to the current literature base of rechallenge cases, and to our knowledge is the most up-to-date systematic review of clozapine rechallenge post CAM. We extend the 34 rechallenge cases described by Richardson et al.[32] and explore the rechallenge process within each case in more depth than in previous reviews.[16,21,27,31] The rate of successful clozapine rechallenges in this study reflected prior systematic reviews that report an average 65% success rate.[16,27,31,32] Across the cases in our systematic review, there were no fatalities amongst the unsuccessful rechallenge cases, nor persisting cardiac morbidity. Richardson et al.[32] highlighted the uncertainty of rechallenge as they described one fatal rechallenge case. As this case did not meet our inclusion criteria, due to no index episode of CAM prior to rechallenge, it was not included in this review.

Despite the publication of numerous successful rechallenge cases, the risk of morbidity and mortality remains high in CAM rechallenge, if appropriate measures are not taken. In balancing risk and maximising the safety of rechallenge, taking a multidisciplinary approach and considering cardiac and psychiatric risks have been recommended throughout the literature.[21,38,42] For individuals undergoing rechallenge, the risk of CAM recurrence was highest within the first four to eight weeks.[50] The time to re-develop CAM amongst unsuccessful cases was sooner in rechallenge (median six days) than initial clozapine treatment (median 18 days). Halawa et al.[42] described a similar situation within a successful case, where two rechallenges within one individual demonstrated earlier recurrence of myocarditis during subsequent clozapine exposure. Redevelopment of CAM within unsuccessful rechallenge cases was not seen beyond 12 days. The reason for the earlier development of CAM features in rechallenge remains unclear. Immune-mediated reactions are not necessarily dose-related and can appear even at low doses, with a prior sensitisation potentially at play.[51] The myotoxic effect of clozapine has been proposed to act in a dose-dependent or rate-titration-dependent fashion and may impact how quickly CAM symptoms appear.[38,52] Alternately, the increased monitoring for CAM recurrence during rechallenge may lead to increased awareness and early detection.

Biomarker monitoring was varied both within and across cases, with baseline pathology prior to rechallenge and then monitoring during the rechallenge, often differing case by case. CRP and troponin were the most frequently utilised pathology measurements and were more commonly tested in successful rechallenge cases. Ronaldson et al.[17] highlight the utility of CRP and troponin in monitoring for CAM. The role of less commonly reported biomarkers (such as BNP, eosinophils, monocytes, CK) as part of monitoring remains unclear from the case data. In the instance of isolated rises in biomarkers during rechallenge cases, dose up-titration was either slowed, paused, or the clozapine was ceased.

Notably, there was variation in the guidance for monitoring regimes across rechallenge cases. To inform rechallenge, cases utilised a mix of published rechallenge protocols, locally developed monitoring regimes, or initiation monitoring protocols that were empirically applied in a rechallenge setting. The protocol proposed by Cook et al.[53] was used as a reference in four cases[38,54] and the protocol proposed by Shivakumar et al.[26] was the reference for our two unpublished cases.[41] An additional three cases[30,55] used rechallenge regimes developed by local or clozapine cardiologists. Thirty-six cases used no protocol, or developed their own, with 36% of these 36 cases referring to the Ronaldson et al.[17] CAM monitoring protocol in their discussions. While this protocol has been increasingly recognised as a standardised model of monitoring for myocarditis in individuals on clozapine, it is not specific to the rechallenge setting, and so if used in rechallenge cases, is being done so empirically.

Risk factors for developing CAM have been proposed in the previous literature,[16,56,57] however, due to highly heterogeneous case reports and limited clinical data, there are few statistically significant factors differentiating successful and unsuccessful cases.[32] Select studies[21,30,58] detailed the use of cardiac medications such as ACEi or BB as a cardioprotective strategy for recommencing clozapine after cardiac toxicity without any difference between outcomes within these cases. Higher starting doses and faster dose up-titrations have been proposed as risk factors for the development of CAM.[52].

Daily clozapine doses of 50 mg were reached at a median of three days in the unsuccessful cases. Australian clozapine initiation guidelines have the majority of consumers reaching 50 mg in four days.[59] Utilising slower up-titration rates was proposed as a desensitisation regime[26] for patients re-trialing clozapine. This, along

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with increased monitoring of inflammatory markers, formed the basis of monitoring for recurrence of CAM as an IgE-mediated hypersensitivity reaction.[20] Recent novel findings in Bellissima et al.'s[60] study suggest clozapine metabolism routes may be altered in individuals with CAM, with an increase in clozapine-N-oxide metabolite compared to N-desmethylclozapine pathways which is potentially related to cardiotoxicity. Monitoring of clozapine levels and consideration of clozapine metabolites during the up-titration process may play a role in recognising early changes in the clozapine levels and pathways associated with CAM.[60].

There have been a number of cases described by Ronaldson et al.[61] where, despite raised biomarkers during the index episode of suspected CAM, the clozapine was continued through the biomarker changes, circumventing the need for rechallenge. This may suggest that it is possible to continue clozapine despite the isolated elevation of some biomarkers in select individuals, however, this is an area that warrants further investigation. Currently, standardised measures for identifying subsyndromal disease or assessing and predicting the severity of myocarditis are limited.

An assumption within our study was that clozapine dosing is linear, and at times the doses within studies were extrapolated using available data, which is a limitation. Another limitation of our study included the relatively small case numbers and the variation in data quality, which needs to be considered when interpreting the findings of this data. The other limitation of our study, which also impacts other systematic reviews in this area, is the inclusion of cases that may be subject to publication bias. There may be additional unpublished rechallenge cases (successful or unsuccessful), making it difficult to determine accurate success rates, safety, and outcomes of clozapine rechallenge following CAM. To assist in reducing selection bias, all rechallenge cases were included in our study, even if there was minimal data in some areas (e.g. monitoring, dose regime, demographics). Thus, our strict inclusion criteria of rechallenge cases specifically following CAM, was a relative strength of our study. Past studies have highlighted that published criteria for clinical diagnosis of CAM were not met in up to 65% of cases[32,62] with suspected CAM. Without clear use of standardised clinical definitions, an accurate reflection of incidence rates[29] and rechallenge outcomes can be affected.[32] It is possible that this may have also affected the cases within our study, and may be a factor in premature clozapine cessation in subsyndromal cases.

One of the key challenges in analysing the data was the inconsistency of data reported in each case report, with very few cases reporting consistent complete data across all domains. Our paper shares this challenge with other systematic reviews. We agree with Bellissima et al.[16] and Knoph et al.[27] as they highlight the need for more standardised and high-quality case studies. As a means of addressing this, a centralised system such as a national database (such as that mandated by government bodies for hematological monitoring of neutropenia and agranulocytosis) may assist in collecting systematic information on attempted rechallenge cases and their outcomes. This could reduce reliance on published case reports as the primary data source for rechallenge practices so that future studies, guidelines, and protocols can be based on a larger database that is less likely subject to publication bias.

For people with TRS with a previous index episode of CAM, successful treatment options can be limited, and rechallenge with clozapine may be an important treatment opportunity. To date, safety concerns have limited systematic research around rechallenge. Case reports and case series have limitations, however, they represent the bulk of published work on CAM rechallenge and can be helpful in capturing the heterogeneity of the illness.[27] Data gathered from the cases demonstrated that rechallenge with clozapine following CAM can be successfully undertaken. Whilst caution must be taken during rechallenge, with increased monitoring, slower dose titrations, and collaborative input from a multidisciplinary team, it is reassuring that clozapine rechallenge may be safe to trial in appropriate individuals. Further studies into published rechallenge protocols utilised in rechallenges would help increase the consistency of monitoring within rechallenge data and evaluation of outcomes. Ongoing research into the utility and application of biomarkers (such as CRP, eosinophils, monocytes) is also warranted.

Conclusion

Despite notable heterogeneity within the rechallenge case data, there were several common themes around CAM rechallenge monitoring and dose titration. Principally, starting at lower clozapine doses with slower up-titration and increased monitoring (clinical, pathology, cardiac imaging) were key findings, supported by previous literature in the area. Similarly, collaborative risk assessment and involvement of cardiology services early were also commonly found within the cases. The use of guidelines may help to improve safety and frequency of trials if rechallenge needs to be considered. There continues to be a lack of evidence-based recommendations for cardiac monitoring in clozapine rechallenge following myocarditis, which may be contributing to individuals not being re-trialed on an efficacious medication. Improving the consistency of information documented in future case reports that are published would assist in strengthening the data that recommendations are based on. From this, further research into robust and evidence-based guidelines and protocols to monitor for CAM recurrence during rechallenge may be possible.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924002219.

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