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Methamphetamine associated Cardiomyopathy: An Addiction Medicine perspective.

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Abstract:

Methamphetamine associated cardiomyopathy (MaCM) is an increasingly recognised serious complication from methamphetamine use. It is characterised as the development of otherwise unexplained heart failure in the context of methamphetamine use.

MaCM predominantly affects a young and vulnerable population with high morbidity and mortality. It is the second leading cause of mortality in patient with methamphetamine use disorder. Our understanding of MaCM pathogenesis is based on observational cohorts and autopsy studies.

Currently, the treatment of MaCM is predicated on abstinence. Medical therapies offer some benefit to a minority of patients, however without abstinence medical therapies are often ineffective. Abstinence is difficult for most patients to achieve; all clinicians require an understanding of MaCM and how to educate patients on the risks of ongoing use. Where available, referral to Addiction Medicine specialists to assist with treatment of Methamphetamine Use Disorder is recommended.

This review aims to: (1) explain the proposed pathologic mechanisms of MaCM (2) summarise recent recommendations of the screening and treatment of MaCM (3) highlight the role of Addiction Medicine in the management of patient with MaCM.

Keywords: Methamphetamine associated cardiomyopathy; Cardiomyopathy; Methamphetamine use disorder; Heart failure; Addiction medicine.

Dear Professor Jeff Szer,

Thank you for considering our manuscript: *Methamphetamine associated Cardiomyopathy: An Addiction Medicine perspective.*

Our revised manuscript will be the first to address from an Addiction medicine perspective Methamphetamine associated Cardiomyopathy and is well suited to IMJ aligning with the aims of promoting improved patient care, in general internal medicine, and hospital medicine.

The major revisions we have made include:

1. Further expanding on the practical challenges that exist for people with methamphetamine use disorders accessing healthcare.
2. Created a table of recommendations a clinician can use when treating patient with methamphetamine use disorder to screen for and minimise risk of MaCM.
3. Clarified the relationship of age and coronary artery disease in MaCM.
4. Addressed general trends of substance use.

The manuscript is original, and this work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part. There are no conflicts of interest to disclose.

Kind regards,

Vincenzo Somma

Acronyms

ACE-I; angiotensin-converting enzyme inhibitors

ARB; angiotensin II receptor blockers

BMI; body mass index

CBT; cognitive-behavioural therapy

cMRI; cardiac magnetic resonance imaging

ECGl; Electrocardiogram

GP; General Practitioner

MA; Methamphetamine

MaCM; Methamphetamine associated cardiomyopathy

MUD; Methamphetamine use disorder

NYHA; New York Heart Association

TTE; transthoracic echocardiogram

(i)Text

Introduction

Harms from methamphetamine (MA) use in Australia are high in prevalence and estimated to cost the Australian community approximately $5 billion annually. [1] Recently, complications of use including methamphetamine associated cardiomyopathy (MaCM) have been gaining increasing recognition. The exact prevalence of cardiac abnormalities associated with methamphetamine use however remains unknown at present. Internationally, heart failure hospitalisations in people who use methamphetamine have increased, and cardiac complications remain the second leading cause of methamphetamine-related mortality in Australia. [2, 3] There are multiple mechanisms underlying the pathophysiology of MaCM, which is a complex entity not deterministically related to either cumulative methamphetamine intake or presence of objective structural damage seen on cardiac imaging. [4] Prognosis is strongly influenced by whether abstinence from MA use can be achieved. [5] Managing individuals who have methamphetamine use disorder can be challenging and there are additional practical complexities to treating those who have MaCM. We provide here an overview of MaCM and how the Addiction Medicine specialty can assist in managing individuals with Methamphetamine Use Disorder (MUD).

Epidemiology of MA use

According to the latest National Drug Strategy Household Survey in 2019, 1.3% of people aged over 14 years used MA in the previous 12 months, and 5.8% reported using MA at some point in their life. [1] The most common age group to use methamphetamine is from 20 to 29-years-old, with the median age of first use being 22 years-old. [1] The most common form of methamphetamine used is crystal methamphetamine (50%) which is the most potent form. [1]

It is reported that around 56% of people with MUD inject methamphetamine, 18% inhale, and 26% both inhale and inject. [6] Intravenous use of MA has increased recently, and now the common "drug injected most often in the past month" (53% in 2021 comparted to 41% in 2020). [7]

Methamphetamine use is a recognised cause of cardiomyopathy and affects a young and often vulnerable population. Overall, patients with MUD have a mortality rate 3-6 times higher than non-methamphetamine users. [8] After MA overdose, cardiovascular disease is the second leading cause of methamphetamine-related death in Australia. [3] MaCM was first recognised in Northern America in the 1970's with reports of new onset heart failure in young patients with MUD. [9, 10] MaCM is becoming more frequently diagnosed and recognised, with hospitalisation rates increasing internationally. An American study demonstrated a 585% increase in hospital presentations from 2008-2018 for MaCM, with 95% being under the age of 65 years old. [2] No Australian data exists for MaCM related hospital presentations. [2] Notwithstanding this, MaCM is becoming more frequently diagnosed in the Australian health context, [11] necessitating the need for greater awareness of this condition and practical strategies for its management.

Pathophysiology

Methamphetamine is cardiotoxic, however the exact pathogenic mechanisms of MaCM are yet to be fully elucidated. Currently, no consensus definition of MaCM exists. Nonetheless, most studies recognise multiple patterns of MaCM, with the most common pattern of MaCM being a dilated and globally impaired left ventricular systolic function. [10, 12] Other commonly described patterns of MaCM include Takotsubo and reverse Takotsubo pattern, attributed to a stress response. [12] MaCM occurs in both chronic and sporadic users of

methamphetamine, indicating that MaCM may not necessarily have a dose-dependent relationship with methamphetamine use. [13] The mechanism by which MaCM develops has been hypothesised to be a multifactorial process, with MA exerting both primary and secondary effects. [13]

Primary effects of methamphetamine use include chronic inflammation and myocardial ischaemia, resulting in direct myocardial wall stress and cardiac myocyte loss. [14] Chronic overstimulation of the sympathetic nervous system, elevated levels of reactive oxygen species, proinflammatory markers (IL-6, IFN-y) and endothelial cell activation has been found in patients with MUD. [14] This eventually leads to apoptosis or replacement of cardiac myocytes with fibrosis, resulting in a dilated cardiomyopathy. [4]

Secondary effects of methamphetamine use on cardiac function result from an increase in systemic levels of serotonin, noradrenaline and dopamine. [15] These can lead to systemic hypertension, coronary artery vasospasm, pulmonary arterial hypertension, arrythmias and dissection of the aorta or coronary arteries. [12] Methamphetamine use induces bouts of subacute hypertension which have been postulated to contribute to MaCM, this includes acute decompensations in patients with established MaCM during hypertensive crisis. [16] These factors also contribute to myocardial wall stress and further deterioration in cardiac function. Both the primary and secondary effects of methamphetamine use place the individual at a higher risk of cardiac contractile dysfunction and the development of a pathological cardiomyopathy. [17]

Methamphetamine use has also been shown to be atherogenic, with plaque accumulation in coronary arteries in the absence of traditional risk factors. [16] An Australian human autopsy

study found 19% of people who use methamphetamines had a degree of coronary artery stenosis at an average age of 38 years old. This compares to only one in six (16%) of the general population of the same age. [3, 16] Furthermore, Westover and colleagues demonstrated a significant association (Odds-ratio 1.61, 95% confidence-interval 1.24-2.04, p-value<0.01) between methamphetamine and acute myocardial infarction. [18] Subacute levels of myocardial ischaemia may contribute to the development of MaCM.

Recommendations for the treatment of MaCM

Consensus on the treatment of MaCM emphases abstinence from methamphetamine use. [11, 13, 15, 16, 19] Abstinence has been associated with improvement in left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class status. A retrospective cohort study of 54 patients (mean age of 51.5 years-old, range of 26-78 years-old) demonstrated benefits of abstinence from methamphetamine use with a NYHA class and LVEF improvement (35.3% abstinent group, vs 10.8% continued use group) over an average of 8 weeks of abstinence (p-value<0.005). [5] A recent review published by Osekowski and colleagues proposed a multidisciplinary approach aligning with the biopsychosocial model of care. [11]

Multidisciplinary approach

Patients with MaCM present a complex clinical picture, all biological, social, and psychological aspects of patient care need to be addressed. [11, 20, 21] When considering a patient initially presenting with acute heart failure and MA use, input will be required from multiple teams. Cardiology to investigate and manage the acute decompensation whilst initiating guideline-based heart failure therapy, Addiction Medicine to manage acute withdrawal symptoms and offer an avenue to a rehabilitation program and often Psychiatry to

manage concurrent mental illness. [11, 22] From a social perspective establishing a support network and incorporating allied health services to attempt to optimise community support services. [11] However, a unified transition between teams addressing all areas of the biopsychosocial model of care is difficult to achieve.

Practical challenges

Significant barriers exist for patients with MUD accessing healthcare. Despite being a health condition, substance use disorder, including MUD, is associated with higher rates of stigma and marginalisation than any other health condition. [6] This results in less focus on physical (including cardiovascular) health and poorer access to investigations and treatment. Furthermore, the characteristics of MUD pose practical challenges in attending treatment. MUD is associated with drug-induced psychosis which can be characterised by delusions (typically paranoia) and or hallucinations and behavioural responses to these, such as disorganisation, agitation, and sometimes aggression. [23] MUD is also associated with cognitive impacts, including impaired maintenance of focus, selective attention, working memory, planning and decision-making. [24] Regulation of emotions, impulse control and flexible thinking are often diminished in MUD and sleep/wake cycles can be erratic. [13] These various patterns of behaviour result in difficulty getting to appointments on time (if at all), difficulty giving a history, difficulty with planning goals and with focussing on working towards them, lower frustration tolerance and poorer ability to consider consequences of actions. These are all difficult, practical challenges for individuals with MUD to access and receive the healthcare they need.

This pattern of behaviour results in low attendance rates to follow-up outpatient appointments. Furthermore, both ECG's and TTE rely on patient cooperation. For patients

who are experiencing methamphetamine-induced agitation or even psychotic symptoms, or for those who are withdrawing from MA, there can be significant difficulty obtaining an ECG or TTE that is interpretable.

Investigations

All patients who are currently using or have a history of methamphetamine use should be screened for MaCM with an electrocardiogram (ECG). [11] A single centre retrospective cohort analysis of 212 patients (mean age 33.4 years-old) found people who use methamphetamine have higher rates of ECG abnormalities when compared to age- and gender-matched controls (71.7% vs 32.1%, p-value<0.0001). [25] Given the high rates of cardiac complications with methamphetamine use, the current recommendation is to refer any methamphetamine-using patient with an abnormal ECG for a formal transthoracic echocardiogram (TTE). [11]

Medical therapy for MaCM.

Achieving adherence to optimal medical therapy is often more difficult for individuals who use MA, especially where there is heavy use of MA. Retention in treatment is typically low and relapse to MA use is high especially in heavy users. [2] Furthermore, as outlined in Osekowski *et al* up-titration of angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin II receptor blockers (ARB) is challenging. This is often due to a lower body mass index (BMI) in patients with MUD. [11] Patients with a low BMI frequently have a lower baseline blood pressure, therefore, increasing the doses of ACE-i and ARBs may lead to hypotension, limiting the maximum dose achieved. [11] There is also a heightened risk of euglycemic ketoacidosis with sodium/glucose transporter 2 receptor (SGLT-2) inhibitors due

to unpredictable eating patterns and concurrent eating disorders that are increased in prevalence in people who use MA. [11, 26]

Advanced cardiac device therapy.

Advanced cardiac device therapy requires careful consideration in the MaCM cohort. Often a range of psychosocial factors preclude users from accessing regular health care after device insertion. One American study demonstrated that of patients with MUD eligible for an implantable cardioverter-defibrillator, only 14% received a device [2] The risk of complications including device associated infection may be considered sufficiently likely to outweigh any benefit. [13] Close follow up is required to monitor patients for signs of such complications. The decision for cardiac devices therefore needs to be made on a case-by-case basis.

Prognosis

Age alone is not a predictor of poor outcomes. Currently the potential for reversibility of MaCM is predicated more on the absence of cardiac fibrosis. [17] Once diagnosed on cardiac magnetic resonance imaging (cMRI), discussion with the individual about the presence of fibrosis must be approached sensitively. The individual may believe the prospect of recovery to be "too late", therefore potentially diminish motivation for abstinence.

Treatment of Methamphetamine Use Disorder (MUD).

For individuals who use MA episodically and hence do not have a MA use disorder ('addiction'), ceasing further use of the drug is achievable. For those with MA Use Disorder (MUD) however, achieving abstinence can be difficult. There are currently no effective pharmacotherapies for MUD (comparable to opioid agonist treatment in opioid use disorder)

[27] There is some interest in combination therapies but response rates at present remain low. [28]

Notwithstanding this, we should not shy away from improving health outcomes for those with MUD. Given the significant burden of disease, it is important that there is public health messaging about MA associated cardiomyopathy so that there is greater awareness of this condition. Public health approaches regarding tobacco and alcohol harms have seen smoking rates in Australia being amongst the lowest in the world and young people are delaying initiation of alcohol use. [29, 30]

In the clinical context, Cardiology and other medical services caring for patients who use MA can provide a Brief Intervention, which involve a screening and assessment of substance use. Such interventions have been proven to be effective in patients with MUD reducing use in one randomised control study. [31] These opportunistic interventions aim to encourage a decrease in consumption or focus on harm minimisation strategies. [32] An example would be enquiring about use patterns (amount, route, frequency, duration of use, pattern of use, and simultaneous other drug use), discussing the association between methamphetamine use and MaCM and suggesting strategies to reduce use. [33] Where injecting drug use is frequent, harm minimisation strategies can also include encouragement of patients to utilise supervised injecting rooms where available.

Where there is more entrenched use of MA, referral to Addiction Medicine specialists where available is recommended. Treatment options depending on the extent of MA use and concomitant neuroadaptation include a range of behavioural interventions (e.g cognitive behavioural therapy, other) that have demonstrated positive outcomes. [20] In some cases, pharmacotherapy may be indicated depending on comorbid mental health conditions.

Conclusion

The historic siloed approach to individuals with substance use and addiction has meant that attention to physical health of people who use drugs is often poor. As overall substance use continues to increase in the Australian community, attending to the physical comorbidities of people who use drugs is imperative, not only for the individual to reach optimal health and wellbeing but also to reduce healthcare costs and maximise the wellbeing of the community. [7, 34] There is a precedent for proactively treating the physical comorbidities in Australia with the continuing successful treatment of hepatitis C in people who use drugs reducing the prevalence and associated complications and impact on quality of life. [35, 36] Notwithstanding the challenges in treating people who use methamphetamine that we have outlined here, we must similarly endeavour to find approaches to improving their health and well-being that work best.

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Recommendations	Practical aspects
ECG	For all patients with a history of Methamphetamine use. If significant abnormalities and/or history suggestive of heart failure, then refer for formal TTE.
Brief-interventions	Enquire about use patterns (amount, route, frequency, duration of use, pattern of use, and simultaneous other drug use). Outline risks of ongoing use, stating risk of cardiac toxicity.
Harm-minimisation	Encouragement to utilise clean needle programs and supervised injecting rooms where available.
Multidisciplinary approach	Early referral to Addiction Medicine, rehabilitation and withdrawal units and contacting drug, alcohol community support and coordination with GP.

Table 1.
Initial recommendations for a patient presenting with a history of Methamphetamine use to screen for and minimise risk of MaCM.
GP; General practitioner, TTE; Transthoracic echocardiogram.