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REVIEW

Methamphetamine-related cardiovascular diseases

Valentin Schwarzbach*, Karsten Lenk and Ulrich Laufs

Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Leipzig, Germany

Abstract

Aims Abuse of crystal methamphetamine (MA) poses a growing problem for health services worldwide. This review summarizes the current literature on the effects of MA on the cardiovascular system.

Methods and results This article is a presentation of a case report and review of the current literature. In Europe, especially the eastern countries and the eastern states of Germany are affected. MA increases the concentration of catecholamines in the synaptic gap leading to euphoria, alertness, and hunger suppression as well as psychiatric and gastrointestinal complications. MA consumption is associated with hypertension, acute and chronic myocardial toxicity, stroke, coronary artery disease, and sudden cardiac death. Although many aspects of the underlying pathophysiology remain unknown, catecholamine-mediated pathologies appear to play an important role. The duration of MA consumption is the most important determinant for the prognosis.

Conclusions Awareness is needed as cardiac complications are important causes of morbidity and mortality in patients with MA consumption. Drug abstinence is the mainstay of therapy, cardiac and other complications should be treated according to the respective guidelines. Incompliance to therapy and frequent relapses are the main challenges for successful treatment. Further research is required to improve the understanding of this rapidly increasing cardiomyopathy.

Keywords Methamphetamine; Crystal; Cardiomyopathy; Heart failure; Europe

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**Correspondence to: Valentin Schwarzbach, Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Liebigstr 20, 04103 Leipzig, Germany. Tel: +49 341 97 20973; Fax: +49 341 97 12659. Email: valentin.schwarzbach2@medizin.uni-leipzig.de*

Historical context

Methamphetamine (MA) was first synthetized in 1893 by Nagayoshi Nagai in Japan.[1] It was sold under the brand name *Pervitin* in the 1930s and 40s in Germany and was widely used as a stimulant by the German military in World War II. It was initially prescribed to treat obesity, narcolepsy, and hay fever and is still approved for the treatment of obesity and attention deficit hyperactivity disorder.[2]

Prevalence and distribution in Germany and Europe

MA is the most frequently abused amphetamine-type stimulant in the world. Its expanding market is shown by the increasing need for patient treatment as well as growing numbers of drug seizures worldwide.[3] MA seizures are increasing in Europe since the year 2002 with an all-time high in 2015 especially in Germany, Norway, Turkey, and the Czech Republic.[4] Patient surveys in Germany show a higher prevalence of MA abuse in the eastern states, especially the ones situated close to the border with the Czech Republic, e.g. Saxonia (*Table 1*). Sewage water analyses in European countries also show the highest concentration of MA in Germany, Slovakia, and the Czech Republic (*Table 2*, *Figure 1*).

Pharmacology and pathophysiology

There are multiple routes of MA administration, smoking of crystalline MA being the most popular one. Other routes include nasal inhalation, swallowing, or intravenous injection. Of the two enantiomers, the (+)-isomer is the biologically more potent and mainly abused one. The weaker (-)-isomer is used as a nasal decongestant.[7] MA itself does not possess direct sympathomimetic properties but leads to an increase in the concentration of monoamines in the synaptic gap by stimulating the release as well as inhibiting the

Table 1 Prevalence of methamphetamine abuse in select German states

Prevalence of methamphetamine abuse in German states	Lifetime (%)	12 months (%)	30 days (%)
Bavaria	1.1	0.4	0.0
Hamburg	0.9	0.4	0.3
Hesse	0.7	0.0	0.0
NRW	0.3	0.2	0.0
Thuringia	1.7	0.8	0.2
Saxonia	2.0	0.3	0.0

Prevalence is shown in (%) per lifetime, 12 months or 30 days respectively. The eastern states, Thuringia and Saxonia, the latter with a border to Czech Republic, show an increased prevalence compared with the western states. Adapted from de Matos *et al.*[5]

Table 2 Wastewater analysis of methamphetamine (MA) in select European cities

City (country)	MA concentration
Chemnitz (Germany)	240.6
Erfurt (Germany)	211.2
Budweis (Czech Republic)	2002
Brno (Czech Republic)	185.7
Dresden (Germany)	180.2
Bratislava (Slovakia)	149.2
Nuremberg (Germany)	94.8
Oslo (Norway)	92.5
Magdeburg (Germany)	85.2
Zurich (Switzerland)	62
Barcelona (Spain)	49
Helsinki (Finland)	46
Vilnius (Lithuania)	39.7
Munich (Germany)	7.9
Athens (Greece)	4
Hamburg (Germany)	3.6
Porto (Portugal)	0.5
Paris (France)	Below quant.

Wastewater analysis of average population normalized loads of MA in select European cities (mg per 1000 inhabitants per day). Adapted from.[6]

degradation and reuptake of dopamine, serotonin, norepinephrine, and epinephrine.[8] These monoamines, especially dopamine, are responsible for the majority of the desired effects like euphoria, alertness, and hunger suppression.[9] The stimulatory effect of MA lasts for hours, compared with minutes in cocaine.[10] At the same time, MA causes multiple psychiatric, neurological, cardiac, and gastrointestinal complications.

Cardiac complications

Histological findings

In rat models with long-term MA administration, histopathogical examinations showed cardiac lesions including atrophy, lysis and necrosis of the myocytes, inflammation, interstitial oedema, fibrosis, and mitochondrial degeneration. These effects were partly reversible after cessation of MA intake.[11–14]

A post-mortem examination of a human heart showed concentric myocardial hypertrophy, extensive myocardial remodelling with perivascular and interstitial fibrosis as well as myocardial scarring due to infarction.[15] Independently of the duration of the MA abuse, endomyocardial biopsies show signs of inflammation by increased numbers of T-lymphocytes and macrophages compared to patients with DCM. There is an increase in perivascular and interstitial fibrosis, the degree of which increases with duration of MA abuse.[16] These histological findings show similarities to other forms of toxic myocarditis, e.g. caused by cocaine and catecholamines.[17]

Acute cardiovascular toxicity

The acute cardiac effects of MA are caused by its sympathomimetic properties and direct cardiotoxicity. They manifest by an increase in heart rate, systolic blood pressure, and respiratory rate over the course of several hours.[18] The cause of direct cardiotoxic effects of MA are still not fully understood, but there is evidence that the formation of free oxygen radicals and nitration of contractile and mitochondrial proteins lead to myocyte degeneration.[19] Acute cardiac decompensation with pulmonary oedema due to malignant hypertension has been reported after MA intake.[20] Contaminants, which may be intermediaries of MA synthesis or deliberately added impurities to cut the drug, may exert additional toxic effects on their own.[21]

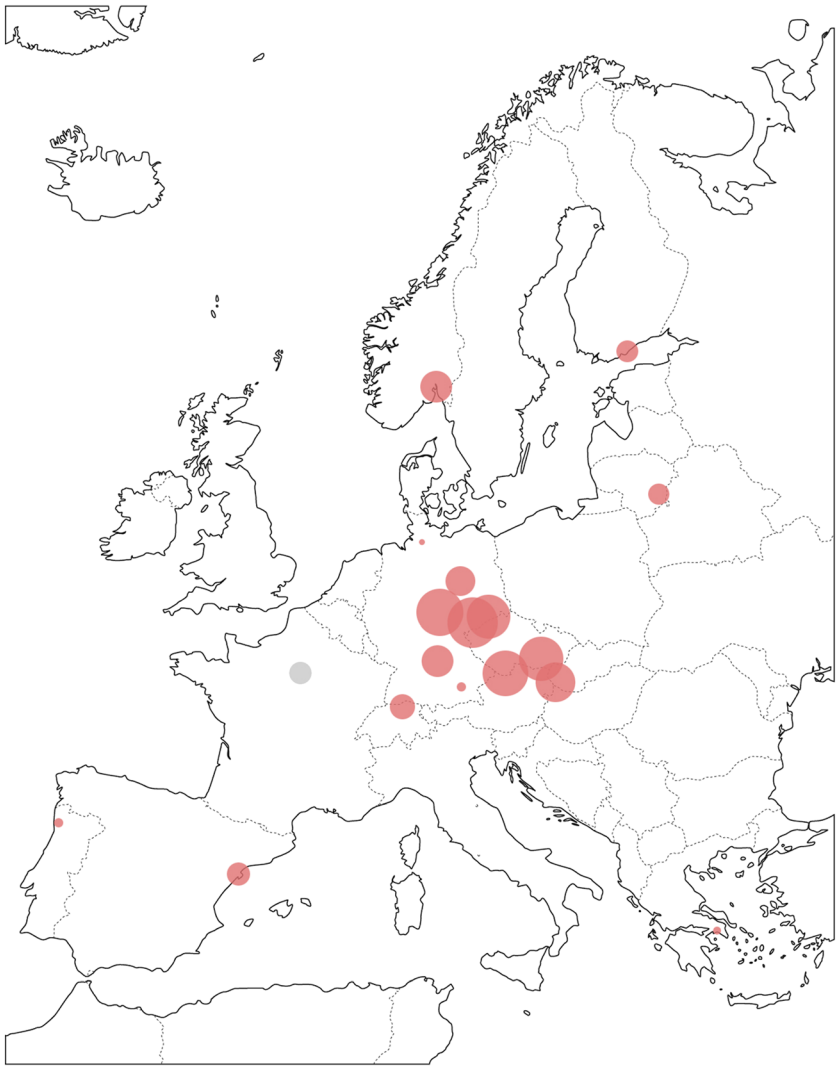
Hypertension related complications

Chronic MA abuse can lead to long-term hypertension and hypertensive cardiomyopathy.[22] There also seems to be a correlation between idiopathic pulmonary hypertension and MA consumption.[23]. MA abuse is the second most common cause for aortic dissection after idiopathic hypertension in the USA.[24]

Heart failure

The first autopsy reports linking MA to left ventricular (LV) heart failure and cardiac death were reported in the 1970s.[25] The first case reports of MA-related reversible dilated cardiomyopathy (DCM) have been published in the 1980s.[25,26] A retrospective case series by Wijetunga *et al.* on patients with a discharge diagnosis of cardiomyopathy and concomitant MA abuse revealed a high percentage (19 of 21 patients) of echocardiographic LV-dilation LV ejection

Figure 1 Wastewater analysis of *methamphetamine* (MA) in select European cities. The size of the dots corresponds to the concentration of MA (see Table *2*)

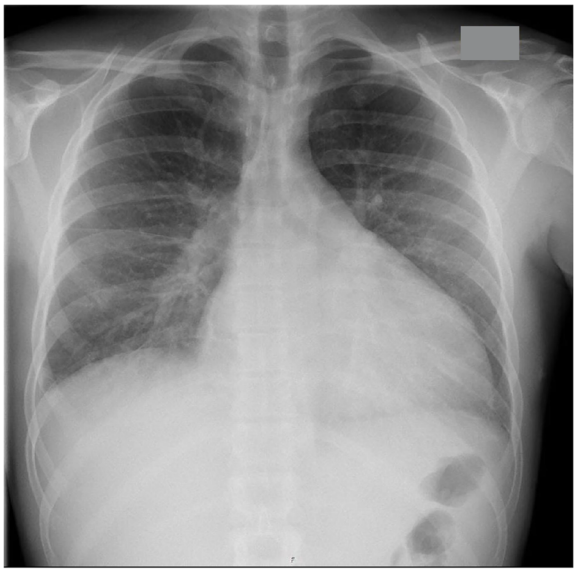


fraction (EF) reduction.[27] Another case series compared echocardiographic features of patients with cardiomyopathy and MA abuse compared with a matched group without MA abuse. Patients with coronary artery and relevant valve disease were excluded. While many characteristics, i.e. gender, age, and obesity were similar, MA abusers had a significantly lower LVEF and more dilated ventricles and atria.[28]

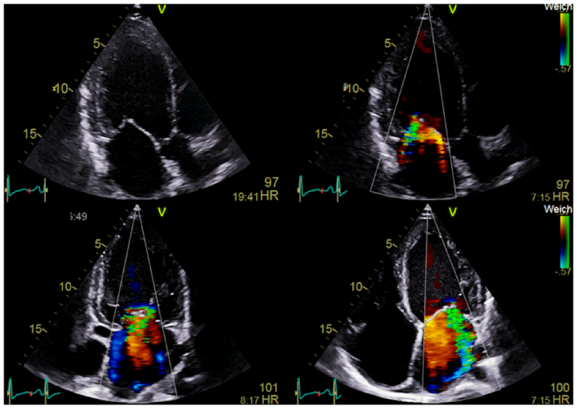
The pathophysiology leading to heart failure still is not fully understood, but several causes appear to be responsible. For one, the constantly elevated level of catecholamines seems to play a major role in the pathogenesis of MA-associated DCM. In agreement with this pathology, cases of catecholamine-induced DCM due to pheochromocytoma are reported, where the LVEF recovered after operative treatment.[29–31] Also, the histological features of MA-associated cardiomyopathy (MACM) and catecholamine-induced DCM have been shown to be similar.[32]

There still is uncertainty about the percentage of patients that develop heart failure or other cardiac pathologies due to MA abuse. A retrospective analysis of patients in an emergency ward showed heart failure in approximately 10% of MA abusers, as determined by an increase in BNP.[33] In a case-control study with 107 cases, MA increased the risk to suffer from cardiomyopathy by a factor of 3.7 in patients under the age of 45 years.[34] CYP2D6 is responsible for the first step of MA metabolism. Correlating to this, a small prospective case-control study showed a, albeit statistically insignificant, trend that individuals with an increased CYP2D6 metabolism were more likely to develop DCM.[35] A clinical case of a patient with MA abuse is depicted in *Figure 2*.

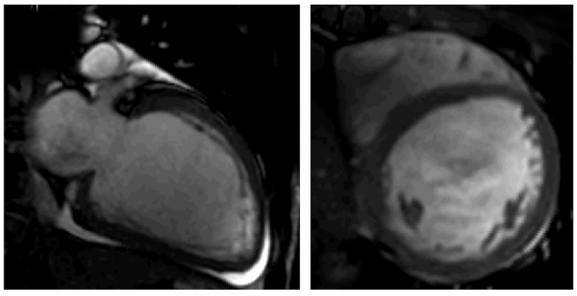
Figure 2 Clinical case report of a patient with frequent MA abuse. A: Chest X-ray showing cardiomegaly and lung congestion at the time of hospital admission. B: Transthoracic echocardiogram showing LV-dilatation and moderate to severe secondary mitral regurgitation due to ring dilatation. C: Diastolic 2 chamber and shortaxis views in cardiac MRI showing LV enlargement without signs of myocardial infarction or inflammation and discrete pericardial effusion.



A Chest X-ray showing cardiomegaly and lung congestion at the time of hospital admission.



B Transthoracic echocardiogram showing LV-dilatation and moderate to severe secondary mitral regurgitation due to ring dilatation.



C Diastolic 2 chamber and short axis views in cardiac MRI showing LV-enlargement without signs of myocardial infarction or inflammation and discrete pericardial effusion.

Fig. 2 The male 23-year-old patient presented himself in our emergency department with upper abdominal pain and cardiogenic shock. The initial physical examination showed a pale, cold and sweaty integument, pulmonary rales, a grade 2 systolic murmur, tachycardia and decreased blood pressure (109/82 mmHg). He reported progressive dyspnea and edematous swelling of both ankles for 2 weeks. There were no known prior diseases nor regular intake of medication. The patient reported consumption of methamphetamine (MA) regularly over the past 5 years as well as concomitant alcohol and tobacco use. He denied the intake of other illegal substances, which was confirmed by drug screening.

Lab testing showed acute renal failure as well as elevated liver enzymes. The initial ECG showed sinus tachycardia (106 bpm) and delayed R-progression. The X-ray showed cardiac dilatation and pulmonary edema (Fig. 2a). Echocardiography revealed a severe global hypokinesia with a left ventricular ejection fraction (LVEF) of 20% and moderate mitral regurgitation (Fig. 2b). The patient was admitted to the intensive care unit and stabilized with inotropic therapy. Coronary heart disease was excluded by left heart catheterization. Cardiac magnetic resonance imaging (MRI) showed no signs of myocarditis or takotsubo cardiomyopathy (Fig. 2c). Thus, the diagnosis of methamphetamine induced cardiomyopathy (MACM) was suggested.

Heart failure medication was initiated according to current guidelines. Furthermore, the patient was equipped with a defibrillator vest. He was closely monitored in our outpatient clinic, where the clinical status was stable, albeit there was no recovery of LV function. After 6 weeks he again was admitted by the emergency service due to dyspnea and edema of the ankles. Echocardiography showed another deterioration of LVEF. The patient admitted to recurring consumption of MA as well as poor medication intake. Furthermore, the defibrillator vest had not been worn regularly. After another week of hospital treatment, the patient was re-compensated and comprehensive outpatient care was re-established.

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Takotsubo cardiomyopathy

There have been case reports of reverse takotsubo cardiomyopathy (r-TTC) with akinesia of the basal areas of the myocardium, in contrast to the more common apical ballooning in TCC. In a study of patients with subarachnoid haemorrhage and TCC, this more uncommon reverse form seemed to correlate with higher levels of catecholamines and younger age.[36,37] Thus, unphysiologically high levels of catecholamines, i.e. after MA consumption, may more often lead to r-TCC. In a retrospective study by Voskoboinik *et al.* on patients with MACM, nearly one third of the patients (6/20) presented with an r-TCC-like pattern of hypokinesia compared with global hypokinesia. These patients had a shorter duration of MA abuse, lower rate of ventricular fibrosis, and better recovery of LVEF during follow-up, suggesting that r-TCC might be an early, reversible form of MACM.[38]

Sudden cardiac death

MA abuse leads to multiple abnormal electrocardiogram results, prolongation of the QTc-interval being the most prominent one. This might explain the higher prevalence of malignant heart rhythm disorders like ventricular tachycardia or torsades de pointes.[39,40] Furthermore, fibrosis is most likely responsible for an increase in shock impedance in patients with an implantable cardioverter-defibrillator.[41]

Coronary artery disease and myocardial infarction

Coronary artery disease is common in MA abusers. Early coronary microcirculation abnormalities and reduced myocardial perfusion can be detected by myocardial contrast echocardiography.[42] In an Australian study of 894 MA-associated deaths, autopsy showed a high prevalence of coronary artery disease (19%), LV-dilatation (26.3%), LV-hypertrophy (19%), myocardial scarring (19.8%) despite the young mean age of 37.9 years.[43] However, there seems to be a high prevalence of myocardial infarction in the absence of coronary artery disease in MA abusers as well. A patient died of myocardial infarction and subsequent cardiogenic shock after smoking MA. Autopsy revealed diffuse myocardial infarction without coronary artery stenosis.[44] In another case report of a young patient, myocardial infarction was attributed to generalized microvascular spasm leading to TIMI-1 flow in all coronary arteries in the absence of coronary stenosis.[45] Spontaneous dissection of multiple coronary arteries leading to myocardial infarction has also been reported.[46]

Stroke

MA intake is associated with both haemorrhagic and ischaemic strokes. In a review of case reports and series, 80% of reported strokes in young patients taking MA were haemorrhagic.[47] This differs from normal stroke populations, where the majority of strokes are ischaemic, even in young patients.[48] Haemorrhagic stroke may be provoked by MA-associated arterial hypertension.[49] Ischaemic stroke on the other hand may be caused by vasoconstriction, vasculitis, or thromboembolism.[50,51] Intracardiac thrombi are reported in up to 33% of MA abusers, which can also lead to coronary occlusions.[16,52] A 10-year follow-up of more than 1300 psychiatric patients with MA abuse and propensity score matched controls showed a significant increase in cerebrovascular and cardiovascular disease, mainly haemorrhagic stroke and arrhythmias.[40]

Diagnosis

Physical examination may show signs of heart failure. In younger patients presenting with heart failure, drug history should be taken, and in case of doubt, urine analysis to screen for drugs should be performed. In patients with known MA abuse, a 12-lead electrocardiogram can reveal signs of cardiac damage and QTc-prolongation. Measurements of BNP can diagnose early stages of heart failure without apparent clinical signs of decompensation. In suspected heart failure, an echocardiography is indicated to assess cardiac function, especially LVEF. 3D speckle tracing imaging markers are useful for early detection of ventricular dysfunction.[53] Contrast echocardiography may be helpful in detecting early microvascular changes and myocardial ischaemia.[42] Left heart catheterization should be performed to exclude coronary artery disease and, in the case of suspected myocarditis, to obtain myocardial biopsies. Right heart catheterization can help diagnose and differentiate the subtype of pulmonary hypertension. Cardiac MRI (CMR) can further help differentiate between cardiac inflammation and other cardiac diseases (i.e. DCM, amyloidosis, storage diseases, etc.), as well as detecting diffuse interstitial fibrosis and myocardial scars as prognostic markers. A limitation of CMR is the relatively low sensitivity in detecting cardiomyopathic forms of myocarditis.[54]

Prognosis

Prognosis is limited by the degree of heart failure due to LVEF reduction, cardiac fibrosis, and complications at the time of diagnosis. Predictors of LVEF recovery are shorter duration of methamphetamine abuse, absence of myocardial fibrosis, smaller left ventricular and left atrial size, and an r-TCC

Table 3 Echocardiographic findings in methamphetamine-associated cardiomyopathy

Parameter	Baseline	Continued abuse	Discontinued abuse
LVEF (%)	19 ± 6	21 ± 4	43 ± 13
LVEDD (mm)	67.1 ± 7.4	68.2 ± 5.5	56.1 ± 6.7

The initially severely reduced left ventricular ejection fraction (LVEF) improves to a moderately reduced LVEF in patients with discontinued abuse, while it stays the same in patients who continue abusing methamphetamine. Analogously, there is a notable reduction in LV end-diastolic diameter (LVEDD) in patients with discontinued abuse, while the LV stays dilated in the continued abuse group. Table adapted from Schuerer et al.[16]

pattern of initial hypokinesis.[16,38] In contrast, those with evidence of myocardial fibrosis and ventricular enlargement have limited scope for recovery. Interstitial fibrosis as determined by an increase in late gadolinium enhancement in cardiac MRI.[55] seems to be an independent prognostic marker. A case report of a patient with severely reduced LVEF but no late gadolinium enhancement showed complete LVEF recovery.[56] This has also been observed in a small prospective study of six patients[57] and correlates to observations made in idiopathic DCM.[58]

Therapy

During acute intoxication with hypertensive crisis, both vasoconstrictive -adrenergic and vasodilative β-adrenergic receptors are activated. Thus, -antagonists should be administered prior to β-antagonists to avoid further increase of blood pressure. Sedation with benzodiazepines can help reduce intrinsic catecholamines. In the long-term, nonselective beta blockers, i.e. carvedilol, should be administered. Complications, like aortic dissection, pulmonary oedema or stroke should be treated respectively.

Cardiogenic shock may require extracorporeal cardiac and lung support. In cases of persistently reduced LVEF after more than 2 months of complete drug abstinence under optimal medical and device therapy, an assist device (LVAD/BiVAD) or heart transplant should be considered.[59] While many acute complications can be treated successfully, strict methamphetamine abstinence is the main challenge of long-time therapy in MACM. In the early stages of the disease when cardiac fibrosis is still mild, moderate to complete recovery of LVEF can be achieved (*Table 3*) This also correlates to an improved functional NYHA-class.[16,60]

Medical therapy for heart failure should be administered according to current guidelines. For patients with severely reduced LVEF, wearable defibrillators, or in case of persistency, the implantation of an implantable cardioverter-defibrillator should be considered, but compliance is a major obstacle in this patient population.

Cardiac thrombi are common in MACM and often cause thromboembolic complications. If diagnosed, anticoagulation should be established. There is no scientific evidence regarding the optimal duration of therapy. An initial anticoagulant therapy of 6 months is recommended by the European Society of Cardiology in thrombi after myocardial infarction, whereas long-term anticoagulation should be considered in case of recurrent thrombi. However, it is unclear if this recommendation can be transferred to thrombi in MACM, as the pathology leading to thrombus formation is different. There are no reliable data for the use of nonvitamin K antagonist oral anticoagulants.[61]

Referral to a medical rehabilitation centre should be recommended to all patients with frequent MA abuse. However, even after a successful initial treatment, relapse numbers remain high. Up to 61% of patients relapse in the first year, another 25% in the following 4 years.[62] This emphasizes the importance of frequent outpatient contacts.

Conclusions

MA abuse has many deteriorating psychological and somatic effects, cardiac complications being among the major factors for morbidity and mortality. Drug abstinence is the mainstay of therapy, cardiac and other complications should be treated according to the respective guidelines. Incompliance to therapy and frequent relapses are the main challenges for successful treatment.

Conflict of interest

None declared.

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