Is the recreational use of MDMA related to the prevalence of toxic cardiac valvulopathy? A cross sectional study between non-, incidental and heavy MDMA users.

Published: 07-06-2022
Last updated: 04-04-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac valve disorders
Study type	Observational non invasive

Summary

ID

NL-OMON52054

Source
ToetsingOnline

Brief title
The prevalence of toxic cardiac valvulopathy in MDMA users

Condition

- Cardiac valve disorders

Synonym
Heart Valve disease, Valvulopathy

Research involving
Human

Sponsors and support

Primary sponsor: OLVG
Source(s) of monetary or material Support: er wordt nog een aanvraag gedaan voor het wetenschapsfonds van het OLVG;echter dit zal hooguit 5% van het budget kunnen opleveren.,uit eigen middelen

Intervention

Keyword: MDMA valvulopathy

Outcome measures

Primary outcome

Moderate to severe valvular regurgitation (futher defined as secondary

outcomes)

Secondary outcome

- Prevalance of heart valve abnormalities (valvulopathy) in group 1 (heavy

users) and group 2 (moderate users) compared to group 3 (non-users):

- Moderate aortic regurgitation

- Severe aortic regurgtitation

- Moderate aortic stenosis

- Severe aortic stenosis

- Moderate mitral regurgitation,

- Severe mitral regurgitation

- Moderate mitral stenosis

- Severe mitral stenosis

- Moderate pulmonary regurgitation

- Severe pulmonary regurgitation

- Moderate pulmonary regurgitation

- Severe pulmonary stenosis

- Moderate pulmonary stenosis

- Moderate tricuspid regurgitation,

- Severe tricuspid regurgitation

- Moderate tricuspid stenosis

- Severe tricuspid stenosis

Confirmation of the hypothesis that heavy use holds a higher risk for heart

valve abnormalities (in line with previous studies)

Study description

Background summary

Several newly developed drugs for the treatment of depression, Parkinson*s disease and obesity have been removed from the market as they appeared to have detrimental effects on cardiac valves, leading to restricted valvular motion that results in regurgitation.1-3 Researchers identified the serotonin 2B (5HT2b) receptor as a mediator of cardiac valvular fibrosis, comparable to carcinoid heart disease and development of primary pulmonary hypertension.4,5 The party drug 3,4 methylenedioxymethamphetamine (MDMA or *ecstasy*) selectively binds to this receptor and produces proliferative actions on human cardiac valvular cells in vitro, comparable to the aforementioned drugs.6 MDMA is a popular drug despite being an illicit substance in most countries. According to the annual report of the national institute of mental health and addiction, approximately 7.7% of Dutch inhabitants have used MDMA in their life, which makes it the second most popular recreational drug after cannabis. MDMA is particularly popular between the age of 20 and 40 years old. In this age group, up to 22.9% of people have used MDMA at least once and up to 13.1% report past-year use. MDMA is mostly used on an incidental base, less than once a month. A small group of approximately 5.2%, reports regular use of several times a month.7 MDMA is linked to cardiac valvular damage in relatively heavy

users in a case-controlled study by Droogmans et al in 2007.8
Cardiac valve pathology such as mitral or tricuspid valve regurgitation is a common phenomenon and affects hundreds of thousands of people in Europe. Its incidence is strongly related to age but is a relatively rare condition in the age group below 40 years old.9

MDMA is a commonly used drug in the Netherlands, slightly increasing over the past few years. It has a relatively low addictive effect and the potential dangers of its use are most probably underreported.7 Possible damage to cardiac valves has been reported in the past.8 Droogmans et al studied a relatively small group (N=29) of very frequent MDMA users and compared them with non-MDMA-users. They found that the use of MDMA was associated with a significantly higher prevalence of regurgitation of mitral, tricuspid and aortic valves. Since incidental use (less than once a month) is more common, it would be of interest to determine if incidental use holds the same potential risk of cardiac valvular damage compared to heavy use (more than once a month).

Study objective

The goal of this study is to determine if MDMA use is associated with a relevant risk of toxic valvulopathy. The popularity of the drug is attributed to its assumed low-risk profile, but these assumptions could be incorrect due to underreporting of adverse events related to the drug and unknown potential side effects such as cardiac valvular damage. Results will be used to gain insight in potentially harmful side effects of MDMA both infrequent and more frequent use. With the widespread use of MDMA as a party-drug and recent interest in its potential benefits on post-traumatic stress disorder, it is important to clarify its potential long-term hazards. We aim to clarify if the potential risk of developing cardiac valvular damage is related to heavy use only or is also increased in persons taking MDMA incidentally.

Study design

GENERAL DESIGN
The proposed study is a cross sectional study using three distinct study groups. These groups are heavy MDMA users (group 1), moderate users (group 2) and none users (group 3). Group 1 will be matched with group 2 and 3 AND group 2 users will be mathed with group 3. People in the age range 20-55 years old will be included because this group is known to have the highest MDMA use (20-35 are mostly current users and >35 years are those who might have had their peak intake in the 90s dance/gabber scene). There is no age restriction. The recruiment of participants is laid out in section F1 and will be matched based on age, sex, education level, country of growing up (due to prevalence of rheumatic fever).

PRE-SCREENING

If, after recruitment, a possibe participant is interested in participation in this study a short phone call will be made asking 2 questions:
1. How much MDMA have you taken cumulatively (lifelong dose) by estimation?
2. Do you have a known cardiac disease? In particular a heart valve disease?

In the case of the absence of a cardiac (valve) disease and an MDMA-use that matched our predifined groups, the participant may proceed to part 1 of the study.
Patient will be send a patient information form (PIF) to their home adress. After this a personalized link (via Castor) will be send to answer a more detailed questionaire.

PART 1 - QUESTIONAIRE
Subjects will be asked to fill out a questionnaire. First they will be asked to specify their medicla history. Known cardiac valvular pathology (i.e. mitral valve prolapse, bicuspid aortic valve), past endocarditis, congenital and ischaemic heart disease could influence results and should therefore be excluded. Other factors of influence are concomitant prescript drug (ab)use and non-prescript drug abuse, therefore subjects will be asked to report on their drug use and abuse. Known prescript drugs that cause toxic valvulopathy are ergot derivatives (f.e. ergotamine in migraine patients), pergolide, benflurorex, fenfluramine and dexfenfluramine. The latter four drugs are no longer available on the market. Long-term use (definied as > 2 weeks) will be an exclusion.

Second subjects will be asked to make an estimated guess (or estimation) about their previous MDMA use (in pills). To aid subjects making this estimate they will be guided to write down their MDMA use per year. Although the analysis is centered around the cumulative amount of pills, we do want to make an estimated cumulative dose in gram. To do so, we use the average MDMA-pill strength per year that is published on the website of Trimbos institute. Finally subjects will be asked about their use of other illicit substances that might act on the 2B (5HT2b) receptor: 2-CB (2,5-dimethoxy-4-bromophenethylamine), 4-FA (4-Fluoroamphetamine), 3-MMC or methaphedrone (3-Methylmethcathinone), 4-MMC or mephedron (4-methyl methcathinone).

After completion of the questionaire both the exclusion criteria and estimated MDMA-use will be checked to see if patient can proceed to the heart ultrasound. It is however possible that a participant can still be excluded after pre-sreening by phone AND filling out the questionaire. For example: MDMA-use too low, >2 weeks use of ergotamine. This option is explained in both the study protocol, the patient information form and will be explained to the participant before filling out the questionaire. We do however expect very few participants to be excluded after the questionaire due to the pre-screening by phone. The results of the participants who are excluded after part 1 will be used in our analysis.

PART 2 - HEART ULTRA SOUND
After a fully filded out questionaire subjects that do not meet any of the exclusion criteria proceed to a full echocardiogram. Thorough evaluation of the function of all heart valved will be done, besides general function/dimenions calculations.

ANALYSIS
Participants in group 1 and 2 will be matched prospectively and individually to a control, based on age and sex. For age distribution groups will be used: 20-25 years, 25-30 years and on untill 50-55 years. After inclusion of a participant in group 1 or 2 we prospectively recrute a sex and age matched control. Participants from group 1 and 2 will be matched to a participant in group 3 in a 1-to-1-setting. Therefore we estimate to screen between 60 and 120 participants in group 3. Some participants in group 3 could serve as a much more than once, but this depends on the caracteristics of this control-person.

The primary outcomes are being described in the section: 'Primary study parameters/outcome of the study'. The primairy and secondary outcomes will be compared be using a Chi Square Test. Univariabele and mutlivariate logistic regression analyses will be done to study the use of MDMA on the primary and secondary outcomes. Also for independent variables (f.e. level of highest education) univariate logistic regression will be done. Variables with a signifcant association ($P < 0.1$) will be included in a stepwise multivariabel logistic regression model to study the corrected effect of MDMA on the primary and secondary outcomes.

FINAL
Every subjects will receive a written report via post within 1 week. In the case of significant heart valve abnormalities (f.e. at least grade 2 out of 4 insufficiency (=leak)) or another unexpected finding the subject will also receive a phone call by one of the study doctors within 1 week. Their GP and/or treating medical specialist will also be informed and a follow-up trajectory will be discussed with the participant.

Last, every subject wiil receive an information letter about the risks of MDMA use. If, judged by the study doctor, a subject might meet criteria of drug abuse, drug counselling will be offered.

Study burden and risks

This study renders no risks for participants. Participation consist of filling out a questionnaire and a 45-minute echocardiographic examination. The possible benefit for any participant is a complete evaluation of cardiac dimensions, function en heart valve (dys-)functioning. In the case of abnormal findings paticipants will both receive phonecall and we will inform their GP or medical specialist (or both) to discuus further follow-up as needed.) (see study

protocol and PIF)

Contacts

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Group 1 (heavy users): circa 1100 pills (+- 200) in a life time
Group 2 (moderate users): circa 550 pills (+- 100) in a life time
Group 3 (never users): never users

Exclusion criteria

Age < 18 years
Pregnancy

Gebruik van ergotamine-derivaten (langer dan 2 weken)
Geschiedenis van hart(klep)ziekte

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2022
Enrollment:	240
Type:	Anticipated

Ethics review

Approved WMO

Date:	07-06-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL76305.100.21