

# 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.

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<b>Ethical review</b>	Approved WMO
<b>Status</b>	Pending
<b>Health condition type</b>	Cardiac valve disorders
<b>Study type</b>	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 (further defined as secondary outcomes)

### Secondary outcome

- Prevalence 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 regurgitation
- 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.<sup>1-3</sup> Researchers identified the serotonin 2B (5HT<sub>2b</sub>) receptor as a mediator of cardiac valvular fibrosis, comparable to carcinoid heart disease and development of primary pulmonary hypertension.<sup>4,5</sup> 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.<sup>6</sup> 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.<sup>7</sup> MDMA is linked to cardiac valvular damage in relatively heavy

users in a case-controlled study by Droogmans et al in 2007.<sup>8</sup>

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.<sup>9</sup>

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.<sup>7</sup> Possible damage to cardiac valves has been reported in the past.<sup>8</sup> 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 matched 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 recruitment 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 possible 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 predefined groups, the participant may proceed to part 1 of the study.

Patient will be send a patient information form (PIF) to their home address. After this a personalized link (via Castor) will be send to answer a more detailed questionnaire.

## PART 1 - QUESTIONNAIRE

Subjects will be asked to fill out a questionnaire. First they will be asked to specify their medical 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, benflurex, fenfluramine and dexfenfluramine. The latter four drugs are no longer available on the market. Long-term use (defined 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 (5HT<sub>2b</sub>) 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 questionnaire 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-screening by phone AND filling out the questionnaire. 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 questionnaire. We do however expect very few participants to be excluded after the questionnaire 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 filled out questionnaire subjects that do not meet any of the exclusion criteria proceed to a full echocardiogram. Thorough evaluation of the function of all heart valves will be done, besides general function/dimensions 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 until 50-55 years. After inclusion of a participant in group 1 or 2 we prospectively recruit 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 characteristics of this control-person.

The primary outcomes are being described in the section: 'Primary study parameters/outcome of the study'. The primary and secondary outcomes will be compared by using a Chi Square Test. Univariate and multivariate 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 significant association ( $P < 0.1$ ) will be included in a stepwise multivariable logistic regression model to study the corrected effect of MDMA on the primary and secondary outcomes.

## FINAL

Every subject 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 will 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 consists 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 and heart valve (dys-)functioning. In the case of abnormal findings participants will both receive a phone call and we will inform their GP or medical specialist (or both) to discuss further follow-up as needed.) (see study

protocol and PIF)

## Contacts

### Public

OLVG

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NL

### Scientific

OLVG

Oosterpark 9  
Amsterdam 1091 AC  
NL

## 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