ISRCTN16259778 https://doi.org/10.1186/ISRCTN16259778

The effects of nitrous oxide ('laughing gas') on thoughts and feelings in healthy people

Submission date	**Recruitment status**	[X] Prospectively registered
27/08/2019	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/08/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
13/08/2021	Other	

Plain English summary of protocol

Background and study aims
Nitrous oxide ('laughing gas') has a variety of effects on mood and thinking. In this study we are looking at whether nitrous oxide produces some of the same effects as ketamine and alcohol. Both of these drugs interact with a brain neurotransmitter receptor called the NMDA receptor, blocking its usual functioning. Nitrous oxide is also thought to have its effects via this receptor, and as such we expect that it will produce similar effects to both alcohol and ketamine.
For example, ketamine produces disturbances in thinking that resemble psychosis, and nitrous oxide may produce some similar (temporary) disturbances in experience. Ketamine also produces effects that resemble alcohol intoxication, so nitrous oxide is expected to share this property with ketamine as well.

Some of these effects might depend on certain personality characteristics or family background, so we are testing this possibility in the current study by asking participants to complete questionnaires about their traits and general moods.

Who can participate?
Women and men aged between 18 and 40, who are healthy and have no psychiatric or physical health conditions that could make nitrous oxide inhalation unsafe.

What does the study involve?
The study involves attending a single session at University College London.

Before arriving at this session, participants will need to complete a screening questionnaire and interview to ensure they are suitable. We will ask about their physical and mental health and their typical (alcohol) drinking habits.
Participants will be randomly assigned to receive either medical air, which is the same as the air we usually breathe, or Entonox, which is the commercial name for nitrous oxide, and contains 50 % nitrous oxide mixed with 50% oxygen. Before inhaling either gas, participants will complete a series of questionnaires about their typical thoughts and feelings, as well as their current thoughts and feelings. They will also be asked questions about whether any of their family members have a history of problems with alcohol use. They will then start inhaling the gas and repeat some of these questionnaires. After completing all of the questionnaires, participants

stop inhaling the gas and sit quietly for 15 minutes. They then repeat a final set of questionnaires. They will be able to leave the lab when at least 30 min has elapsed since they stopped gas inhalation.

What are the possible benefits and risks of participating?
Participants are reimbursed, but there are no personal health benefits associated with taking part. However, by taking part, participants will be helping us understand how nitrous oxide and similar drugs work, and how these might eventually be used to treat people with psychological disorders. As such, participants usually find this kind of study interesting and rewarding.

The research is considered to be low risk. However, as with any study involving the use of medications, it is not possible to eliminate all risks. There are no known long-term risks associated with the study, however, in the short-term, participants who receive nitrous oxide gas might experience some acute side effects such as dry mouth, numbness, nausea and vomiting and dizziness. Because nitrous oxide leaves the body quickly after inhalation stops, these effects reverse quickly. Participants will remain in the department for at least 30 min after the inhalation stops to ensure all effects have worn off.

Where is the study run from?
The study is run from the research department of the Clinical Psychopharmacology Unit, University College London, which is located at 1-19 Torrington Place, London.

When is the study starting and how long is it expected to run for?
The approximate start date for the study is 4th Sept 2019. We expect the study to run for about 5 months.

Who is funding the study?
The study is funded by the UK registered charity Find a Better Way.

Who is the main contact?
Professor Sunjeev Kamboj, sunjeev.kamboj@ucl.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
V1

Study information

Scientific Title
The effects of nitrous oxide on psychosis-like and psychedelic experiences in healthy volunteers: a single-blind randomized experimental study

Acronym
N/A

Study objectives
1. We hypothesise that due to its NMDA receptor antagonist properties, inhalation of 50% nitrous oxide (N2O; 'Entonox') will produce a temporary psychosis-like state in healthy individuals, reflected in elevated scores on the Psychotomimetic States Inventory (PSI; Mason et al, 2008) during N2O inhalation relative to baseline, with no appreciable 'pre-to-during inhalation' change in the medical air group. In addition, we predict a pattern of responding on an adapted version of the Questionnaire of Altered States of Consciousness during inhalation of N2O (but not medical air) that resembles the pattern seen during ketamine infusions (Studerus et al, 2010). These psychedelic effects will only be measured once (during gas inhalation) and compared descriptively to previously published findings (Studerus et al, 2010). Both psychosis-like and psychedelic effects are expected to reverse rapidly (return to baseline) upon termination of inhalation of N2O (by the 15 min post-inhalation time-point).

2. We hypothesise that subjective effects of N2O will resemble those produced by alcohol. We predict that participants will rate their experiences of N2O as similar to alcohol (Krystal et al, 1998). Those with experience of alcohol as well as cannabis (a psychotomimetic) and/or cocaine (a stimulant) will rate the similarity between the effects of N2O and alcohol higher than the similarity between the effects of N2O and cannabis or cocaine. Only participants in the N2O group will also show increased sedative and stimulant effects on the Biphasic Alcohol Effects Scale (BAES-brief) during inhalation relative to pre-inhalation.

3. We hypothesise that bipolar phenotype will moderate the subjective response to N2O in a similar manner to the phenotypic moderation of the response to alcohol (Yip et al, 2012). Specifically, we predict that participants expressing a bipolar phenotype (high scores on the Mood Disorders Questionnaire; Hirschfeld et al, 2000) will show lower sensitivity to the subjective effects of N2O during inhalation than participants with the 'no-bipolar' phenotype.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2019, University College London Research Ethics Committee (Research Ethics Office, Office of the Vice-Provost (Research), University College London, 2 Taviton St, London WC1E 6BT; 020 7679 8717 extension 28717; ethics@ucl.ac.uk), ref: 3901/001.

Study design

Randomised (non-clinical), single blind, placebo-controlled experiment

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Psychosis-like, psychedelic and alcohol-like states induced by nitrous oxide in healthy volunteers

Interventions
Medical air (placebo, BOC, UK) or Entonox (BOC, UK), which is a premixed gas containing 50% N20 and 50% oxygen.
For hypothesis 1 (psychosis-like and psychedelic effects) and hypothesis 2 (alcohol-like effects), the primary between-subjects factor is Group, with two levels (N2O; medical air). The within-subjects factor (Time) has three levels (pre-inhalation, on-gas, post-inhalation). Fifty participants will be equally and randomly assigned to Group using a random number generation procedure (using a combination of RAND(), RANK(), RANK/n and CEILING.MATH functions in Excel). These 'non-purposively' recruited participants will be assigned to Group (medical air placebo: n=25; N2O: n=25) without reference to scores on trait measures and will form the sample used to address hypothesis 1 (psychosis-like and psychedelic effects) and hypothesis 2 (alcohol-like effects). An additional n=30 participants will be purposively recruited to examine hypothesis 3, based on high 'trait' scores (>= 7) on the Mood Disorders Questionnaire (MDQ). These n=30 high-scoring participants will contribute to one level ('bipolar') of an additional between-subjects factor: 'Phenotype', and will also be equally and randomly assigned to N2O and medical air using the same randomization procedure as above (medical air: n=15; N2O: n=15). 'Non-bipolar' participants (the other level of the Phenotype factor) will be the n=30 (medical air: n=15; N2O: n=15) lowest scoring participants from the initial n=50, non-purposively recruited sample.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Medical air (placebo, BOC, UK) Entonox (BOC, UK; premixed as 50% N20 : 50% oxygen)

Primary outcome(s)
Psychosis-like/Psychedelic effects of N2O
1. Psychosis-like ('psychotomimetic') states will be assessed using the Psychotomimetic States Inventory (PSI) total and subscale scores (particularly 'Delusory Thinking', 'Perceptual Distortions', 'Cognitive Disorganization', and 'Paranoia'). The PSI will be administered pre-, during and 15 min after gas inhalation.
2. Altered states of consciousness will be assessed using the 42-item version of the Questionnaire for the Assessment of Altered States of Consciousness (Studerus et al., 2010) administered only on-gas.

Alcohol-like effects of N2O
1. Similarity of current subjective state to (previously experienced) subjective effects of alcohol,

cannabis and cocaine, will be assessed using the Sensation Scale (0-100 visual analogue scale; Krystal et al, 1998) assessed pre-, on-gas and post-inhalation
2. Equivalence in (N2O-induced) intoxication to a specific amount of alcohol will be assessed using the Number of Drinks Scale (NDS; Krystal et al, 1998) at pre-, on-gas and post-inhalation time-points.
3. Subjective stimulant and sedative effects of nitrous oxide will be assessed using the Brief Biphasic Alcohol Effects Scale (B-BAES; Rueger et al, 2009) assessed pre-, on-gas and post-inhalation.
4. General subjective drug effects will be assessed using the 'feel high' and 'feel effect' items of the Drug Effects Questionnaire (DEQ; Morean et al, 2013), per Yip et al's (2012) study on alcohol and bipolar phenotype. Secondarily, hedonic and anti-hedonic effects of gas inhalation will be assessed using the 'liking' and 'disliking' items, and motivational effects, using the 'wanting more' item of the DEQ. The former four items will be assessed pre-, on-gas and post-inhalation (+ 15 min), and 'wanting more', only on-gas and post-inhalation.

Key secondary outcome(s))
Additional measures below are potentially important covariates/moderators (especially the MDQ scores) or cofounding factors (rather than 'outcomes' per se) that we wish to assess for similarity between groups at baseline or test in exploratory analyses:
1. State dissociation will be assessed using the Clinician Administered Dissociative Symptoms Scale (self-report items; Bremner et al 1998), pre-, on-gas and post-inhalation.
2. 'Trait' dissociation symptoms will be assessed with the Brief Dissociative Experiences Scale (DES-B; modified for DSM-V by Dalenberg and Carlson, 2010) – pre-inhalation only.
3. Impulsivity will be assessed with the Barratt Impulsivity Scale 11-Brief (Steinberg et al, 2013) – pre-inhalation only.
4. Historical and recent subjective response to alcohol will be assessed using the Subjective Response to Alcohol measure (Schuckit 1984) – pre-inhalation only.
5. Bipolar phenotype will be assessed using the Mood disorders Questionnaire (MDQ; Hirschfeld et al, 2000) – pre-inhalation only.
6. Schizotypy will be assessed with the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) short form; unusual experiences subscale (Mason et al, 2005) – pre-inhalation only.
7. Problematic alcohol use will be assessed using the Alcohol Use Disorders Identification Test (AUDIT) – pre-inhalation only.
8. Recent alcohol use (previous week) will be assessed using the Timeline Follow-back diary method - pre-inhalation only.
9. Family history of alcohol problems will be assessed using a Family History of Alcohol Problems family tree method - pre-inhalation only.
10. General mood will be assessed using the Depression, Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995) - pre-inhalation only.

Completion date
06/12/2019

Eligibility

Key inclusion criteria
1. Age: 18-40
2. Fluency in written and spoken English
3. Consumes alcohol as social drinker
4. For hypothesis related to moderation of subjective effects by bipolar phenotype, participants will be high scores (>=7) on the Mood Disorder Questionnaire

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex
All

Total final enrolment
80

Key exclusion criteria
1. Are pregnant or are likely to become pregnant during the study or breastfeeding.
2. Suffer from any major physical health disorder
3. Are currently seeking/receiving treatment for any psychiatric condition
4. Have asthma or any breathing difficulty (including sleep apnoea)
5. Have a cardiovascular condition or a fitted pacemaker
6. Have any liver or kidney disorder
7. Have had a ‘collapsed lung’
8. Have difficulties metabolising vitamin B12
9. Have anaemia
10. Have history of stomach ulcers
11. Have high or low blood pressure
12. Have a current ear or sinus infection or a bad cold
13. Have epilepsy
14. Have ever had neurosurgery
15. Are diabetic
16. Have had any recent dental work or dental infection/inflammation
17. Have had any adverse reaction to nitrous oxide in the past
18. Use recreational drugs more than once a week
19. Are unable/unwilling to abstain from drugs and alcohol for 24 hours prior to the study

Date of first enrolment
04/09/2019

Date of final enrolment
02/12/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London
Clinical Psychopharmacology Unit
Research Dept Clinical, Educational and Health Psychology
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Find a Better Way

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon reasonable request from Professor Sunjeev Kamboj (sunjeev.kamboj@ucl.ac.uk), Principal Investigator. The data will be available from approximately Jan 2021. Data will include relevant group allocations and outcome variables and will be anonymised.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/07/2021	13/08/2021	Yes	No