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PENINSULA MEDICAL SCHOOL
UNIVERSITIES OF EXETER & PLYMOUTH

PenTAG

HTA 07/64/01 (HTA Short Reports)

Protocol

1. Title of the project

The harmful health effects of recreational ecstasy: a systematic review of observational evidence

2. Name of TAR team and project lead

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3. Plain English Summary

Street-drugs known as *ecstasy* have been sold for about twenty years in the UK. The active substance that such tablets contain – or purport to contain – is 3,4-methylenedioxymethamphetamine (MDMA). MDMA does not exist in nature; it can only be made chemically. Shortly after consumption, MDMA releases chemicals in the brain that tend to bring about a sense of euphoria, exhilaration, and increased intimacy with others. In the UK, MDMA has been a Class A illegal substance for thirty years. This means that it is classified amongst the most dangerous drugs, and serious penalties are imposed for possession or supply. Most people who take ecstasy also use other legal and illegal drugs, sometimes at the same time. Ecstasy is commonly taken in nightclubs and at parties, and is very often associated with extended sessions of dancing.

Along with the pleasurable effects sought by users of MDMA, it has become clear that the drug can cause a range of unintended harms. In the short term, the most serious dangers arise when MDMA interferes with the body's ability to maintain a constant temperature. In severe cases, multiple organ failure can develop, and this can prove swiftly fatal. To counteract this danger, ecstasy users are advised to drink plenty of fluid. However, some people over-compensate, drinking excessive amounts, and a condition can result in which the excess fluid leaks into the brain, causing it to swell, often with fatal consequences. A variety of other adverse events have been reported in the immediate aftermath of MDMA consumption, including heart failure, brain haemorrhage, and liver failure.

Consumption of MDMA may also have long-term consequences, especially as regards users' mental health. People who have taken ecstasy in the past may have increased susceptibility to depression, and their memory may also be affected. There are other possible psychiatric effects, some of them serious.

This project will systematically review the medical literature detailing the harms to human health from ecstasy. Electronic databases will be searched for journal articles describing the incidence and impact of adverse events. The identified material will be analysed and summarised. Consideration will be given to the features of the evidence that may make its interpretation complex (for example: to what extent is it possible to isolate the long-term harms of MDMA from those of the other substances that users have almost always taken?) If several papers report the same kind of numerical information, this data will be combined by meta-analysis. An effort will also be made to analyse factors that might make some types of user more or less likely to suffer an adverse event.

4. Scope of the review

4.1. Review question

What are the harmful health effects of taking 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) for recreational use?

4.2. Background

Ecstasy is the common street-name for drugs that contain – or purport to contain – 3,4-methylenedioxymethamphetamine (MDMA) as their active ingredient. Following the convention of Gowing and colleagues,[1] the term *ecstasy* is used here to denote the drug as it is sold on the street , whereas *MDMA* refers to the known chemical substance.

Pharmacology

MDMA is an entirely synthetic chemical belonging to the amphetamine family, a group of phenethylamines. Several substances that are closely related in chemical structure are also commonly used as recreational drugs:

- amphetamine ("speed", "whizz")
- methamphetamine (MA; "crystal meth")
- paramethoxyamphetamine (PMA)
- 3,4-methylenedioxyamphetamine (MDA)
- 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA; "Eve")
- 3,4-methylenedioxy-phenyl-*N*-methylbutanamine (MBDB)

Drugs sold as "ecstasy" frequently contain one or more of these substances, instead of or in addition to MDMA.[2] The intended effects for which ecstasy-users take the drug are described in terms of euphoria, exhilaration, and a sense of increased intimacy and empathy with others.[3] The neuropharmacological mechanisms by which these effects are produced involve the release of extracellular serotonin and dopamine,[4] neurotransmitters that are commonly associated with the mood and pleasure systems of the brain.

The physiological effects of MDMA in humans have been studied in controlled conditions. Heart-rate rises to a peak an average of 20-30 beats per minute higher than baseline[5-7] approximately an hour after consumption of doses similar to those taken recreationally. Blood pressure increases over a similar period (systolic by 25-40mmHg, diastolic by 10-20mmHg).[8-10] Body temperature also rises (by 0.3-1.0°C), but this effect is less immediate, with a peak several hours after consumption.[11-13] The apparently non-linear nature of MDMA pharmacokinetics has been emphasised; blood concentrations of MDMA rise disproportionately as dosage is increased.[14]

History

The first documentary record of the synthesis of MDMA is the 1912 German patent application of Merck pharmaceuticals in relation to haemostasis,[15] but it wasn't tested on humans until 1960.[16] Following very sporadic reports in the 1970s, recreational use of MDMA became more widespread during the 1980s,[17] with discussion proliferating in the popular press in 1985.[18] The term *ecstasy* first appeared in print in reference to MDMA in 1985[19] and in the British media in 1987.[20]

The US Drug Enforcement Administration classified MDMA as a Schedule 1 controlled substance with effect from 1st July 1985,[21] In the UK, it had already been criminalised; a statutory instrument of 1977, without naming MDMA in particular, categorised all ring-substituted phenethylamines as Class A substances under the Misuse of Drugs Act[22].

In the UK, reported ecstasy consumption has remained relatively stable over the past decade, with somewhere in the region of 2% of 16-59 year-olds reporting ecstasy use in the preceding 12 months.[ONS crime survey] This makes it the third-most used illegal drug in the UK . It has been estimated that somewhere between 500,000 and 2,000,000 doses of ecstasy are consumed each week in the UK.[23]

Usage

The overwhelming pattern of ecstasy usage is as a part of polydrug consumption.[24] In a 2003 survey of UK ecstasy-using respondents also reported extensive concomitant use of alcohol (88%), amphetamines (83%), cannabis (82%), cocaine (58%) and amyl nitrate (51%), and there was also some use of LSD, ketamine, fluoxetine, crack cocaine, herbal highs and sildenafil. In addition, various substances were used in the "comedown" period following ecstasy consumption, most notably cannabis (82%), alcohol (60%), benzodiazepines (18%) and heroin (2%).

Ecstasy tablets as sold on the street contain a variable amount of MDMA, ranging from none to around 150mg.[25] As noted above, some tablets contain MDEA, MDA and/or amphetamine in addition to or instead of MDMA. Ecstasy tablets may also be "cut" with unrelated substances. Many of these are pharmacologically weak (e.g. caffeine, paracetamol); however there are reports of stronger psychoactive substances (e.g. atropine, opiates, phenylbutanamine and dextromethorphan).[26] One US source analysed tablets in 2005-2007 and found them to have approximately a 1-in-3 chance of containing only MDMA, MDMA along with other active ingredients, or no MDMA at all.[27]

As a result of these factors, it is not possible to isolate exposure to MDMA in particular in any individual history or in characteristics across cohorts. Even if there were such a thing as an identifiable group of individuals whose ecstasy consumption alone distinguished them from the general population, it would still be impossible to ascertain to which chemicals they had been exposed, and at what dosage.

Safety

Reports from investigators assessing the psychotherapeutic potential of MDMA in 1986 suggested that the drug was "apparently physically safe", despite some "undesirable" effects.[28] Within a year of such claims, the first reports of ecstasy-related deaths appeared in the medical literature.[29] In the UK, the first reported fatalities came in 1991.[30;31] Over the past twenty years, a wide variety of fatal and non-fatal complications have been ascribed to consumption of ecstasy.

4.2.1. Acute harms

4.2.1.1. Major syndromes

The most critical acute complications of MDMA consumption are, in a majority of cases, related to two well recognised syndromes, each involving serious derangement of homeostasis leading to multiple organ failure: hyperthermia and hyponatraemia.

Hyperthermia

Derangements of thermoregulation are a widely reported feature of MDMA toxicity,[32] with temperatures as high as 43°C reported in some cases.[33-37] In this context, the association between MDMA use and prolonged dancing may be important, since core temperature rises during intensive exercise.[38]

The physiological manifestations of MDMA-induced hyperthermia are similar to those seen in severe heatstroke.[39] The most noteworthy effects are Rhabdomyolysis,. disseminated intravascular coagulopathy (DIC),acute renal failure (ARF) and acute liver failure.

Hyponatraemia

When the hyperthermogenic properties of MDMA are combined with intense physical activity, profuse sweating inevitably results, and substantial amounts of sodium can be lost in perspiration. This problem is significantly compounded by the tendency of MDMA users to drink large quantities of water The combination of sodium-loss and excess water consumption may also be exacerbated by excess fluid retention (due to inappropriate secretion of antidiuretic hormones and/or impairment of renal function[40]). The resultant hyponatraemic state sees a fall in serum osmolar pressure, allowing intracellular displacement of water, the most hazardous result of which is cerebral oedema.[41]

The early clinical manifestations of hyponatraemic cerebral oedema are headache and nausea, progressing to confusion and seizures[42-45] If not corrected, the syndrome will commonly progress to tentorial hemiation, respiratory arrest, cerebral hypoxia and death.

Subgroup effects may be an issue. Regardless of cause, hyponatraemia is known to be most hazardous in women, especially during menstruation.[46]

4.2.1.2. Isolated acute harms

Acute cardiovascular dysfunction

Tachycardia is an invariable response to MDMA consumption, and is the most frequently reported clinical symptom in series detailing acute admissions in accident and emergency departments.[47;48] There are reports of MDMA-related myocardial infarction[49-52] and sudden cardiac death.[53] The importance of excluding concomitant use of other drugs (especially cocaine, which is very well known to induce critical cardiovascular dysfunction) has been emphasised.[54]

Acute neurological dysfunction (seizures)

Seizures are a recognised manifestation of both hyponatraemia and hyperthermia (see above). Cases have also been reported of MDMA-induced seizures which apparently do not involve either of these underlying causes.[55]

Intracranial haemorrhage

There are several reports of intracranial haemorrhage following consumption of MDMA. Such events are commonly associated with pre-existing cerebrovascular vulnerabilities (e.g. aneurysm[56;57] or arteriovenous malformation[58;59]); however cases have also been reported in which no such features were identified.[60;61]

Respiratory dysfunction

Chest pain secondary to pneumomediastinum (leakage from the airways into the mediastinum; also known as mediastinal emphysema) is a relatively commonly reported condition in those presenting for medical attention following MDMA consumption.[62-74] Less frequently, pneumothorax[75;76] and pneumopericardium[77] have also been reported.

Acute liver failure

Critical hepatic dysfunction is a notable consequence of hyperthermia (see above), and extensive hepatic necrosis is an invariable post-mortem finding in MDMA deaths.[78] In addition, it is well established that MDMA-induced acute liver failure can also occur without thermoregulatory dysfunction.[79-89] This type of acute hepatic failure develops over a slightly longer period than in hyperthermic liver failure, with cases becoming symptomatic a matter of days, rather than hours, after MDMA ingestion.

Renal failure and other urinary tract abnormalities

Occasionally, MDMA-induced kidney dysfunction can occur in the absence of hyperthermia or hyponatraemia. Such cases are frequently associated with severe hypertension.[90-92]

Rhabdomyolysis

A few cases of isolated rhabdomyolysis without evidence of hyperthermia have been reported.[93;94]

Acute ophthalmic injury

There are reports of ocular problems arising from MDMA consumption, including retinal haemorrhage,[95], keratopathy,[96] glaucoma,[97] diplopia,[98] and myopia.[99]

4.2.2. Long-term harms

For all potential long term harms, it is extremely difficult to disentangle the long-term effects of MDMA use from those of the other legal and illegal substances with which the histories of users are invariably confounded.[100]

4.2.2.1. Neuropsychiatric sequelae

While short-term depression of mood in the few days following MDMA use is a common finding in qualitative[101;102] and observational[103] literature, the long-term neuropsychiatric effects of MDMA use are the subject of much research and are widely believed to be irreversible.[104] Some biochemical analyses have shown depletion of serotonin metabolites in the cerebrospinal fluid of human MDMA users, from which permanent impairment of serotonergic function is inferred.[105] The impact of MDMA consumption on dopamine activity has been a more controversial topic. A variety of clinical manifestations may result. Studies have most commonly examined the impact of MDMA use on depression, neurocognitive impairment (with a particular focus on both short- and long-term memory), psychomotor dysfunction, and psychotic symptomatology.

Depression

It is hypothesised that, if MDMA use compromises serotonergic function, long-term consumption can be expected to result in chronic depression of mood.[106]

Neurocognition

It is suggested that recreational MDMA use is associated with deficits in general neurocognitive function,[107] with particularly strong evidence of short- and long-term memory impairment.[107-109]

Psychomotor symptoms

Psychomotor symptoms, such as tremor and even Parkinson's disease, appear to be more common in those with a history of MDMA use.[110 111-115]

Psychosis and other psychiatric disorders

Paranoia and anxiety are recognised characteristics of the short-term experience of MDMA.[102;116;117] Specific persistent psychiatric abnormalities lasting beyond the acute phase are also recorded.

4.2.2.2. Other long-term harms

Dental damage

Trismus and bruxism are very frequent characteristics of MDMA intoxication[118], and excessive toothwear can result. The problem may be exacerbated by consumption of carbonated drinks, which is common.[119]

Long-term susceptibility to seizure

There is some discussion about whether long-term exposure to MDMA predisposes users to epilepsy.[120]

5. Methods for systematic review of evidence

5.1. Inclusion / exclusion criteria

The relevance of all evidence will be appraised with respect the following criteria:

5.1.1. Population

Included:

- Users of recreational drugs in the UK or in populations relevant to the UK

Excluded:

- Animal studies
- Non-drug-using volunteers enrolled in prospective research

- Gamma-hydroxybutyric acid (GHB, "liquid ecstasy")

5.1.2. Exposures

Included:

- Recreational use of substances shown or believed by the investigator(s) to contain MDMA

Excluded:

- Use of street-drugs shown or believed by the investigator(s) not to contain MDMA, whether referred to as "ecstasy" or not
- Therapeutic use of MDMA
- Generic drug-using populations in which it is not possible to isolate a subgroup with exposure to MDMA in particular

5.1.3. Comparators

Some uncontrolled evidence will be considered in the review, where appropriate (see below). Where comparative evidence is reviewed, studies with comparator arm(s) meeting the following characteristics will be eligible:

Included:

- Recreational users of drugs other than MDMA
- Non-drug-users

5.1.4. Outcomes

Included:

- Death
- Acute, clinically observable health harms, including (but not limited to)
  - hyperpyrexia
  - hyponatraemia
  - acute cardiovascular dysfunction
  - acute neurological dysfunction (seizures)
  - acute renal failure / anuria
  - acute liver failure (including "subacute" liver failure and hepatitis)
  - intracranial haemorrhage
  - respiratory dysfunction (including pneumomediastinum and pneumothorax)

  - rhabdomyolysis
  - disseminated intravascular coagulopathy
  - acute ophthalmic injury (including retinal haemorrhage, keratopathy, glaucoma, diplopia, myopia)
- Long term, clinically observable health harms, including (but not limited to)
  - neuropsychiatric sequelae, including
    - depression
    - psychosis
    - memory impairment
    - disorders of neurocognition
    - psychomotor symptoms
  - dental damage

Excluded:

- Surrogate measures of harm (e.g. neuroimaging studies, biochemical markers), where there is no explicit correlation to observed effect
- Biochemical indices of MDMA consumption (e.g. testing for MDMA use in blood or hair samples)
- Studies reporting therapeutic measures for adverse events without providing data on individuals suffering such complications
- Subjective measures of psychostimulation (i.e. studies of the drug's intended short-term intoxicative effects)
- Indirect harms
  - accidental injury where ecstasy consumption is detected/implicated
  - health consequences of high-risk sexual behaviour contributed to by ecstasy consumption
  - birth defects secondary to maternal exposure to MDMA

5.2. Methods

Except where otherwise specified, the general methods of the review will follow the guidance on the conduct of systematic reviews published by the Centre for Reviews and Dissemination.[121]

5.2.1. Identification of evidence

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

5.2.1.1. Search strategy for electronic databases

A comprehensive search syntax using indexed keywords (e.g. MeSH, EMTREE) and free-text terms will be developed. This will build upon the search syntax devised and used for the scoping searches (*Appendix 10.1*).

5.2.1.2. Databases to be searched

The electronic databases that will be searched include: MEDLINE, EMBASE and PsycINFO (all via Dialog DataStar); PubMed (limited to recent publications and in-process citations); Web of Knowledge; the Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register); DARE; NHS HTA database. Simple keywords (e.g. "Ecstasy"; "MDMA") will also be used to consult research registers, to identify any relevant prospective studies.

5.2.2. Inclusion of relevant evidence

The outputs of searches will be considered against the prespecified inclusion/exclusion criteria, with a sample of citations screened by a second reviewer, to appraise validity of assessment. Studies that can confidently be identified as not meeting eligibility criteria on the basis of title and abstract will be excluded. The full texts of all other papers will be obtained. Two reviewers will independently assess whether these studies fulfil the inclusion criteria, with disagreements resolved by consensus.

5.2.2.1. Papers in languages other than English

Due to the time restraint of the project, only studies published in English will be included in the review.

5.2.2.2. Meeting abstracts

Reports published as meeting abstracts will only be included in the review if sufficient methodological details are reported to allow critical appraisal of study quality.

5.2.3. Methods of analysis/synthesis

5.2.3.1. General approach

Initially, all included evidence will be reviewed to establish a taxonomy of reported outcomes. For each outcome, the available evidence will be categorised in a predefined hierarchy of research design:

- **Level I:** *Pre-existing systematic research syntheses* (systematic reviews, meta-analyses, syntheses of qualitative data).

- **Level II:** *Controlled observational studies* (cohort studies, case-control studies, etc.).
- **Level III:** *Uncontrolled observational evidence* (case reports and case series).

Where it is adequately designed and conducted (see below for methods of critical appraisal), Level I evidence will be preferred. Any such synthesis of primary research can be expected to include consideration of all relevant Level II evidence, if it is appropriately comprehensive. Accordingly, where reasonable-quality Level I evidence is available for a given outcome, Level II evidence will only be considered to the extent that it supplements the pre-existing syntheses. For example, Level II studies that post-date the higher-level evidence will be reviewed and appraised. Where possible and appropriate, attempts will be made to extend any quantitative analyses contained in Level I evidence to include such additional evidence. Where no adequate Level I evidence is identified for a given outcome, any Level II evidence will be systematically reviewed. The quality of research will be appraised and described, and findings reported. Where possible and appropriate, quantitative synthesis of study outcomes will also be undertaken (for methods, see below). A brief tabulation and/or summary of Level III evidence will be provided.

Where neither Level I nor Level II evidence is available, Level III evidence will be systematically surveyed.

5.2.3.2. Critical appraisal of evidence

The internal validity of included studies will be assessed using methods appropriate to study design.

Level I: systematic research syntheses

Systematic reviews of observational evidence will be appraised with reference to a quality assessment instrument adapted from the recommendations of the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) proposal.[122]

Level II: Controlled observational studies

Cohort studies and case-control studies will be appraised using a bespoke quality assessment instrument, which will be constructed with reference to recommendations made by Levine and colleagues (1994),[123] Downs and Black (1998),[124] the NHS Centre for Reviews and Dissemination (2004)[121] and Mallen and co-workers (2006).[125]

Level III: Uncontrolled observational studies

Case series and case reports will be appraised using a bespoke quality assessment instrument, which will be constructed with reference to the findings of Dalziel and colleagues (2005).[126]

5.2.3.3. Data extraction

Data will be extracted using a bespoke database. Recorded information, where available, will include:

- Study design (e.g. design, country, setting, dates, length of follow-up)
- Details of study participants, including
  - Baseline demographics (e.g. age, gender)
  - Previous exposure to ecstasy and other legal and illegal substance)
- Details of exposure, including
  - Details of ecstasy consumed (e.g. number of tablets, MDMA content, other substances contained in tablets)
  - Other substances consumed (e.g. alcohol, other recreational drugs)
- Outcome data, including
  - Quantitative data describing key study outcomes
  - Inter-cohort comparisons

All extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.2.3.4. Quantitative synthesis

Where it is possible and appropriate, meta-analysis will be carried out using random-effects models by default. If there is statistical evidence of inter-study homogeneity and no reason to suspect clinical heterogeneity, sensitivity analyses using fixed-effects models will be undertaken. STATA software will be used to pool results and estimate an overall effect measure. Heterogeneity will be explored through consideration of the study populations, methods and exposures, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Small-study effects (including publication bias) will be assessed and quantified.

5.2.3.5. Subgroup effects

For all outcomes, consideration will be given to the possibility of differential effects existing in subgroups (e.g. by age-group, by gender, by exposure to other substances, etc.) Where quantitative synthesis is undertaken, stratified analyses and meta-regression, using potential predictors of effect size as covariates, will be considered.

6. Expertise in the review team

6.1. Peninsula Technology Assessment Group

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in

2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is part of the Peninsula College of Medicine and Dentistry within the Universities of Plymouth and Exeter.

6.2. Team members

The PenTAG team members who will undertake the project have previously produced reports for NICE, the Health Technology Assessment Programme and the Department of Health. These projects have included Technology Assessment Reports, National Guidelines, and short reports. The members of the project team and their role in the project are listed below.

Mr Gabriel Rogers Associate Research Fellow	▪ responsible for project coordination ▪ responsible for drafting the protocol ▪ contributor to devising the search strategy ▪ contributor to review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) ▪ contributor to drafting report (all sections) ▪ responsible for compiling and editing report
Dr Julian Elston Academic Specialist Trainee in Public Health / Honorary Research Fellow	▪ contributor to review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) ▪ contributor to drafting report (results; discussion)
Ms Paula Younger Electronic Resources Librarian[1]	▪ responsible for devising the search strategy ▪ responsible for conducting the literature searches ▪ contributor to drafting report (methods; results)
Ms Ruth Garside Research Fellow	▪ co-responsible for project direction ▪ contributor to drafting report (executive summary; discussion)
Dr Margaret Somerville Principal Lecturer and Consultant in Public Health	▪ co-responsible for project direction ▪ contributor to drafting report (executive summary; discussion)
[1] Exeter Health Library, Royal Devon and Exeter NHS Foundation Trust (1st Floor, Peninsula Medical School Building, Barrack Road, Exeter. EX2 5DW)	

7. Competing interests of authors

None.

8. Timetable

The report will be delivered to NCCHTA by 20 December 2007.

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10. Appendix

10.1. Preliminary search strategy

The following search was run in Medline only (via PubMed) on 15th August 2007, with 2,204 hits identified. The review's final search strategy will build upon this approach and syntax.

```
"n-methyl-3,4-methylenedioxyamphetamine/adverse effects"[MH]
OR
   (("n-methyl-3,4-methylenedioxyamphetamine"[MH] OR MDMA[TW] OR Ecstasy[TW])
   AND (
         (
         (hyperthermia[TW] OR "fever"[MH] OR pyrexia[TW] OR "fever"[TW] OR "Heat
            Exhaustion"[MH] OR "Heat Stress Disorders"[MH] OR heatstroke[TW] OR
            heat stroke[TW])
         OR (hyponatremia[TW] OR hyponatraemia[TW] OR "hyponatremia"[MH])
         OR ("seizures"[MH] OR seizure*[TW] OR fit[TW])
         OR ("cardiovascular system"[MH] OR cardiovascular[TW] OR "heart"[MH] OR
            cardiac[TW] OR heart[TW])
         OR ("intracranial hemorrhages"[MH] OR brain haemorrhage[TW] OR brain
            hemorrhage[TW])
         OR respiratory[All Fields]
         OR (mediastinal[TW] OR pneumomediastinum[TW] OR (intra-alveolar[TW] AND
            pressure[TW]))
         OR (ophthalm*[TW] OR "cornea"[MH] OR cornea*[TW])
         OR ("tooth"[MH] OR tooth*[TW] OR teeth*[TW] OR "bruxism"[MH] OR
            bruxism[TW])
         OR ("liver"[MH] OR liver[TW] OR "hepatitis"[MH] OR hepatitis[TW])
         OR ("death"[MH] OR death*[TW])
         OR (rhabdomyolysis[MH] OR rhabdomyoly*[TW])
         OR (hyponatremia[MH] OR hyponatremia[TW] OR hyponatraemia[TW])
         OR (Kidney[MH] OR Kidney[tw] OR renal[tw] OR nephro*[tw])
         OR (Hematologic-diseases[MH] OR (disseminated[tw] AND intravascular[tw]
            AND coagul*[TW]) OR DIC)
         OR ("Mental Disorders"[MH] OR depress*[TW] OR neuropsych*[TW] OR
            psychopatholog*[TW] OR neurocogniti*[TW] OR cogniti*[TW] OR
            psychiatric[TW] OR panic*[TW] OR delus*[TW] OR memory[TW] OR motor[TW]
            OR psychomotor[TW] OR attention[TW] OR concentration[TW])
         )
      OR
         ("street drugs/adverse effects"[MH]
         OR "substance-related disorders/epidemiology"[MH]
         OR "Designer Drugs/adverse effects"[MH])
      )
   )
```

No study design filters or language restrictions applied