The harmful health effects of recreational ecstasy

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

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Executive summary

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Executive summary

Background

Street drugs known as 'ecstasy' have been sold for about 20 years in the UK. The active substance that such tablets contain – or purport to contain – is 3,4-methylenedioxymethamphetamine (MDMA). Shortly after consumption, MDMA releases chemicals in the brain that tend to bring about a sense of euphoria, exhilaration and increased intimacy with others. It is thought to be the third most commonly used illegal drug in the UK after cannabis and cocaine, with estimates suggesting that between 500,000 and 2 million tablets are consumed each week. 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, a range of adverse events have been reported – some fatal – and consumption of MDMA may also have long-term consequences, especially with regard to users' mental health.

Objectives

This review aims to address the question: 'What are the harmful health effects of taking ecstasy (MDMA) for recreational use?' It does not examine the harmful indirect and/or social effects, such as effects on driving and road traffic accidents and the consequences of any effect MDMA may have on sexual behaviour.

Methods

The following databases were searched using a comprehensive search syntax: MEDLINE, EMBASE, PsycINFO (run 19 September 2007) and Web of Knowledge (run 7 October 2007). The search outputs were considered against pre-specified inclusion/exclusion criteria; the full text of all papers that could not confidently be excluded on title and abstract alone was then retrieved and screened. Only studies published in English were included. Meeting abstracts were included only if sufficient methodological details were given to allow appraisal of study quality. Studies were categorised according to a hierarchy of research design, with systematic research syntheses (Level I evidence) being preferred as the most valid and least open to bias. Where Level I evidence was not available, controlled observational studies (Level II evidence) were systematically reviewed. If neither Level I nor Level II evidence was available, uncontrolled case series and case reports (Level III evidence) were systematically surveyed. Data extraction was undertaken by one reviewer and a sample checked by a second.

Synthesising Level II evidence posed substantial challenges due to the heterogeneity of the included studies, the number and range of outcome measures reported, the multiplicity of comparisons (differing ecstasy exposures, differing comparator groups) and outcomes, repeated measures and the observational nature of the data. Analyses were stratified for current and former ecstasy users, with separate analyses for control groups using other illegal drugs but not ecstasy (*polydrug controls*) or controls naïve to illegal drugs (*drug-naïve controls)*. Random-effects meta-analyses were used throughout. Heterogeneity was also explored through study-level regression analysis (meta-regression). Where a sufficient number of studies had reported identical outcomes, they were meta-analysed on their original scale. Other outcome measures were grouped into broad domains and effect sizes expressed as standardised mean differences in order to combine data derived from multiple instruments. Objective and self-reported outcome measures within each domain were analysed separately.

For the Level III evidence, only narrative synthesis was possible.

Results

Of 4394 papers identified by our searches, 795 were reviewed in full and 422 met the inclusion criteria. Five systematic syntheses, 110 controlled observational studies and 307 uncontrolled studies

were included. The controlled observational studies exclusively investigated the chronic harms, mainly neurocognitive and psychopathological, associated with ecstasy use. Sixteen case series based on national and regional registries and databases were concerned with deaths from ecstasy (nine were UK based). Additional information on deaths was available from the General Mortality Register (GMR) and the Special Mortality Register collated by the National Programme on Substance Abuse Deaths (np-SAD). The remaining case series and case reports concerned both fatal and non-fatal acute harms.

Most of the included studies were small and subject to biases in selection of subjects and controls, measurement and reporting of confounders and outcomes.

Previous research syntheses (Level I evidence)

For each identified Level I synthesis, it was difficult to ascertain the exact methods adopted and evidence included. Three reviews reported worse performance for ecstasy users compared to controls in a variety of neurocognitive domains (attention, verbal learning and memory, non-verbal learning and memory, motor/psychomotor speed, executive systems functioning, short- and long-term memory). A fourth study reviewed self-reported depressive symptoms and found that ecstasy users had increased levels compared to controls. The final synthesis was primarily concerned with the acute intoxication effects of ecstasy rather than health harms. In all analyses, the effect sizes seen were considered to be small.

Controlled observational studies (Level II evidence)

Of the 110 controlled observational studies included, there was one prospective study, the Netherlands XTC Toxicity (NeXT) study, which recruited a cohort of participants likely to start using ecstasy and followed them for a year. Those who started using ecstasy were then compared to a group of matched controls who had remained ecstasy-naïve. Ecstasy-exposed participants had poorer performance in some memory tests, although the absolute test scores for both cohorts were comfortably within the normal range. Other tests suggested an association between ecstasy exposure and certain aspects of sensation-seeking, but there was no evidence of an effect on depression or impulsivity. The cumulative dose of ecstasy consumed was small (median 3–6 tablets).

The remaining Level II evidence consisted of cross-sectional studies only. Data were directly pooled for seven individual outcomes. Six were common measures of immediate and delayed verbal recall, in which ecstasy users performed significantly worse than polydrug controls. Effect sizes appeared to be small, with the mean scores for each group falling within the normal range for the instrument concerned. No difference was seen between ecstasy users and polydrug and drug-naïve controls in the remaining measure, IQ.

A total of 915 outcome measures were grouped into broad outcome domains as suggested in the literature and after consultation with expert advisers. For 16 of these meta-outcomes, there were sufficient data for meta-analysis: immediate and delayed verbal and visual memory, working memory, sustained and focused attention, three measures of executive function (planning, response inhibition and shifting), perceptual organisation, self-rated depression, memory, and anxiety and impulsivity measured objectively and subjectively. Ecstasy users performed significantly worse than polydrug controls on all outcome domains with the exception of executive function (response inhibition and shifting) and objective measures of impulsivity. Fewer comparisons were possible with drug-naïve controls, with statistically significant effects seen for verbal and working memory and self-rated measures of depression, memory and impulsivity. With both control groups, former ecstasy users frequently showed deficits that matched or exceeded those seen among current users.

The small effect sizes seen were not consistently modified by any study-level demographic variables. There was little evidence of a dose–response effect: studies reporting heavier average use of ecstasy did not provide more extreme effect measures than those consisting of lighter users, and there was no demonstrable effect of length of abstinence from ecstasy. When assessing the impact of inter-arm differences on results, no consistent effect was seen for imbalances in age or gender. However, in several cases, it appeared that imbalances in intelligence between cohorts may have been important. Use of other drugs also appeared to modify effects: alcohol consumption proved the most consistent effect modifier, with increased exposure in ecstasy-exposed populations

apparently reducing the magnitude of deficits across a range of neurocognitive outcomes.

For the remaining outcome domains, there were insufficient data for quantitative synthesis and the results were summarised narratively. For psychopathological symptoms, there was a significant deficit for ecstasy users compared to polydrug controls in the obsessive–compulsive domain only, with greater deficits seen in comparison to drug-naïve controls. In a few studies, ecstasy users have been shown to have higher levels of subjectively rated aggression than drug-naïve controls. It was not possible to draw clear conclusions about the possible effects of ecstasy consumption on dental health, loneliness, motor function or sleep disturbance.

Case series and case reports (Level III evidence)

Registry data from the np-SAD and GMR are not directly comparable due to differences in data sources and recording of drug use. The GMR (1993–2006) suggests that there were, on average, 17 deaths a year where ecstasy was recorded as the sole drug involved (2.5% of all deaths ascribed to a single drug) and another 33 per year where it was reported as co-drug use. Ecstasy-associated deaths appear to have increased up to 2001 but to have stabilised thereafter. In the 10 years to 2006, the np-SAD recorded an average of 50 drug-related deaths in which ecstasy was present (69 in 2006; 5% of the total for the year). Ecstasy was believed to be the sole drug implicated in an average of 10 deaths annually over the same time period. According to this registry, the typical victim of an ecstasy death is an employed white male in his twenties, who is a known drug user co-using a number of other substances. Nearly half of ecstasy-related deaths occur on a Saturday or Sunday night.

Published case series and case reports document a wide range of fatal and non-fatal acute harms, often very selectively. Two major syndromes are most commonly reported as the immediate cause of death in fatal cases: hyperthermia (with consequences including disseminated intravascular coagulation, rhabdomyolysis and acute liver and renal failure) and hyponatraemia (commonly presenting with confusion and seizures due to cerebral oedema). Ecstasy users presenting with hyponatraemia have invariably consumed a large amount of water. We found 41 deaths relating to hyperthermia reported in the literature and 10 from hyponatraemia (all women).

Other acute harms associated with fatal cases include cardiovascular dysfunction, neurological dysfunction (seizures and haemorrhage) and suicide. Acute renal failure and subacute liver failure can occur without association with hyperthermia. All these presentations were also seen in non-fatal cases, alongside an additional range of symptoms including acute psychiatric effects, urinary retention and respiratory problems including pneumothorax and pneumomediastinum.

There are difficulties in estimating taken dose of MDMA from the available literature, and it is not clear why some people seem to have acute, even fatal, reactions to doses that are commonly tolerated in others.

Discussion

The evidence we identified for this review provides a fairly consistent picture of deficits in neurocognitive function for ecstasy users compared to ecstasy-naïve controls. Although the effects are consistent and strong for some measures, particularly verbal and working memory, the effect sizes generally appear to be small: where single outcome measures were pooled, the mean scores of all participants tended to fall within normal ranges for the instrument in question and, where multiple measures were pooled, the estimated effect sizes were typically in the range that would be classified as ‘small’.

However, there are substantial shortcomings in the methodological quality of the studies analysed. Because none of the studies was blinded, observer or measurement bias may account for some of the apparent effect. There is a suggestion of publication bias in some analyses, and we saw clear evidence of selective reporting of outcomes.

Selection bias is an inevitable problem: due to the observational nature of all relevant evidence, there is no guarantee that the cohorts being compared were not subject to differences in areas other than exposure to ecstasy. This effect will have been exaggerated in those studies comparing ecstasy-exposed participants to drug-naïve controls; in these instances, it is impossible to isolate the effect of ecstasy exposure from the impact of other substances. Within-study imbalances in intelligence and the use of other substances, particularly alcohol, appeared to explain some of the effects seen. We suggest that the apparently beneficial

effect of alcohol consumption may be explained in two ways: either alcohol may mitigate the hyperthermic effects of ecstasy in the acute setting, attenuating damage to the brain, or ecstasy users who co-use alcohol may represent a population of more casual ecstasy takers than those who tend not to drink.

Although the NeXT study suggests that small deficits in memory may be secondary to ecstasy exposure, all other included studies were cross-sectional in nature; without evidence of the temporal relationship between exposure and outcome, it is difficult to draw any causal inferences.

We did not find any studies directly investigating the quality of life of participants, and we found no attempts to assess the clinical meaningfulness of any inter-cohort differences. The clinical significance of any exposure effect is thus uncertain; it seems unlikely that these deficits significantly impair the average ecstasy user's everyday functioning or quality of life. However, our methods are unlikely to have identified subgroups that may be particularly susceptible to ecstasy. In addition, it is difficult to know how representative the studies are of the ecstasy-using population as a whole. Generalising the findings is therefore problematic.

Ecstasy is associated with a wide range of acute harms, but remains a rare cause of death when reported as the sole drug associated with death related to drug use. Hyperthermia and hyponatraemia and their consequences are the commonest causes of death, but a wide range of other acute fatal and non-fatal harms are reported. Due to the poor quality of the available evidence, it is not possible to quantify the risk of acute harms in any meaningful way.

Research recommendations

Large, population-based, prospective studies are required to examine the time relationship between ecstasy exposure and neurocognitive deficits and psychopathological symptoms.

Further research synthesis of the social and other indirect health harms of ecstasy would provide a more complete picture. Similar synthesis of the health harms of amphetamines generally would provide a useful comparison.

Future cross-sectional studies will only add to the evidence-base if they are large, as representative as possible of the ecstasy-using population, use well-validated outcome measures, measure outcomes as objectively as possible with researchers blind to the ecstasy-using status of their subjects, report on all outcomes used, and provide complete documentation of possible effect modifiers. Cohorts should be matched for baseline factors, including IQ and exposure to alcohol.

The heterogeneity of outcome measures used by different investigators is unhelpful: consensus on the most appropriate instruments to use should be sought. Investigators should collect data directly reflecting the quality of life of participants and/or attempt to assess the clinical meaningfulness of any inter-cohort differences.

A registry of adverse events related to illegal intoxicants presenting to medical services (akin to the 'yellow card' system for prescription medicines) would enable useful estimation of the incidence of harmful effects of ecstasy in comparison to other substances.

Future case reports of acute harms of ecstasy are unlikely to contribute valuable information to the evidence-base. Where novel findings are presented, care should be taken to report toxicological findings confirming the precise identity of the substance(s) consumed by the individual(s) in question.

Publication

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NIHR Health Technology Assessment Programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/64/01. The protocol was agreed in October 2007. The assessment report began editorial review in April 2008 and was accepted for publication in August 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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