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MDMA and mephedrone: current psychobiological models of ‘Ecstasy’ and ‘m-cat’, and future human research needs.

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Abstract.

Thirty years ago, 3,4-methylenedioxymethamphetamine or MDMA was a novel psychoactive substance (NPS), and since then empirical knowledge of its psychobiological effects in humans has increased substantially. It is now known that recreational users can suffer from a wide range of psychobiological deficits, in neurocognition, memory, information processing, vision, pain, oxidative stress immunocompetence, neurohormonal integrity, sleep, homeostasis, and psychiatric well-being. Functional deficits may remain after several years of abstinence. Ten years ago mephedrone was a novel psychoactive substance, and recent studies have generated some limited knowledge about its psychobiological effects, although many areas of uncertainty remain. This review will outline current scientific knowledge on each drug, and suggest areas for future research. One crucial area is the effects of mephedrone on human pregnancy, since taking MDMA during pregnancy can impair subsequent child development.

Introduction.

This paper is an extended version of a keynote paper given at the European Conference on Novel Psychoactive Substances (NPS), held at the Fielder Centre in Hertfordshire University, on November 15th-16th 2016. The conference was funded by the European Union, with the aim of disseminating the latest information on the clinical, pharmacological, psychosocial, legal and other aspects of the many new

psychoactive drugs being used across Europe and the world. My own paper focused on current extensive knowledge about the psychobiology of recreational MDMA, and a comparison with the more limited empirical knowledge on mephedrone. One key aim was to illustrate how our theoretical understanding about MDMA had increased dramatically over the past 15 years, since research had revealed many novel areas of psychobiological deficit. The main focus of my talk was the empirical research conducted by my research group at the University of East London (pre-2004), then at Swansea University (2004-present), and latterly as a visiting Professor to the Centre for Human Psychopharmacology in Melbourne (2008-present). However research findings from many other groups were also covered. Recently we have undertaken comparative studies with established stimulants such as cocaine (1), and methamphetamine (2). This paper will conclude with two empirical comparisons between recreational Ecstasy/MDMA and mephedrone (3,4). The aim was to investigate the similarities and differences in their psychobiological profiles, and propose topics for future research.

MDMA or 'Ecstasy': a broad overview

MDMA or 3,4-methylenedioxymethamphetamine, is a methamphetamine derivative and powerful CNS stimulant. It first became popular as a recreational drug during the mid-1980s, when it was given the street name of 'Ecstasy' (5-8). Around that time MDMA was a 'novel psychoactive substance', although that particular label was not employed for another twenty years. In one of the first descriptions of its psychopharmacological effects, Shulgin (9) suggested that MDMA would not become a psychosocial drug of abuse, since it lost its subjective efficacy when taken repeatedly. However despite its strong chronic tolerance, many recreational users followed a pattern of increasing self-dosing, accompanied by stronger and more damaging side-effects (10,11). The deteriorating cost-benefit ratio with MDMA leads to voluntary drug cessation – an unusual and possibly unique pattern for any psychoactive drug (11-14). This pattern helps to explain why MDMA is not often seen as a drug of dependency. However, while many users quit on their own, other young Ecstasy/MDMA users still need professional help from drug addiction centres (15-17).

In acute terms, MDMA is powerful metabolic activator, which causes increased body temperature in thermally controlled laboratory conditions (18,19). It can lead to greater thermal stress and hyperthermia in dance clubbers, although there can be considerable variation in these thermal changes in the real world (20, 21, 90). In cold conditions recreational users may cool-down excessively, so when returning from night clubs in Wintery conditions, some users become hypothermic with adverse medical consequences (23,24). The Hypothalamic Pituitary Adrenal (HPA) axis can also be acutely overstimulated by MDMA, with cortisol levels increasing by up to 800% in MDMA-using dance clubbers (20). Furthermore the regular use of Ecstasy/MDMA can lead to chronic disruptions in the HPA axis. In a recent study we collected hair samples from 101 young volunteers, and measured the amount of cortisol laid down in their hair over the recent 3 months. The regular users of Ecstasy/MDMA displayed a highly significant group mean 400% increase in hair cortisol, when compared to non-user controls, whereas the light users showed non-significant increase of around 50% (21). Cortisol is also known as the 'stress hormone', and several groups have shown changes in cortisol patterns and/or increased stress levels. Scholey et al (25) found that drug free Ecstasy/MDMA users reported significantly higher levels of stress, than similar aged non-user controls. Wetherell and Montgomery (26) showed that the cortisol awakening response, and other indications of cortisol secretion, were altered in drug-free Ecstasy/MDMA users, especially under conditions of high environmental stress. The various indications of change to the HPA axis have been outlined in recent reviews (27,28), while potential neurohormonal topics for future research have also been suggested (29). The contributory role of oxytocin also needs to be further studied, since oxytocin may be involved in the positive psychosocial effects of MDMA (30,31). Furthermore, nasal oxytocin may potentially comprise a safer compound for drug assisted psychotherapy (30-32,91).

The acute mood effects of MDMA can be extremely euphoric, although as with all CNS stimulants, negative moods may also be intensified (34,35). Several years ago, we found that initial MDMA experimenters who stopped taking it reported less positive moods, than those who progressed to regular usage (36). An almost identical pattern has been found with young cannabis experimenters, since those who reported more positive initial responses to cannabis, displayed a far greater tendency to

become regular cannabis users (37). Indeed there are a number of interesting functional and psychobiological similarities between the sedative drug herbal/spice cannabis, and the stimulant drugs MDMA and mephedrone; these were outlined in Parrott et al (38). Hence an interesting topic for future research, not just for MDMA, but with other recreational drugs such as mephedrone, cocaine or cannabis, is to further investigate this individual variation in initial reactions to the psychoactive drug. In many studies this variation will be embedded with the overall group values, and hence often ignored, yet it may provide a fruitful topic for future research. Another related issue is negative mood reactions. Many studies into CNS stimulant drugs have focused on positive mood gains, yet negative mood abreactions occur with all stimulants - including MDMA (39). It is important for future studies to include *adverse mood state scales* within their assessment batteries, since some past studies have only included positive mood scales – and hence found only positive outcomes (see review in: 40).

MDMA is a powerful metabolic activator; indeed being a methamphetamine derivative, it comes from one of most powerful classes of all recreational stimulant drugs. The acute effects of MDMA have been outlined in several reviews (41-44). The strong CNS activation it generates is the basis for the Bioenergetic Stress model of MDMA, which is described in the following articles (12,14,45-49). The Bioenergetic Stress model for humans was based on laboratory animal research (50,51). This explanatory model notes that the heightened activation in recreational users, will often represent the combined sympathomimetic overstimulation caused directly by MDMA, along with the stimulatory environmental conditions at dance clubs (47,52). This model generates a number of interesting questions for future research. How do the co-factors of environmental activation: prolonged dancing, loud music, social crowding, sweating/dehydration, and body/brain overheating, heighten the basic metabolic overactivation caused by MDMA (14,47,49,53,54). What are the key individual difference factors, such as personality characteristics or genetic profiles, of those who seem most susceptible to this overactivation? Why are females more susceptible to the development of acute hyponatraemia (55)? It is also known that MDMA causes programmed cell death or apoptosis in laboratory animals, and increases oxidative stress in recreational users (56). MDMA has also been tested as drug for cancer therapy - due to its ability to damage human cells (see the relevant

medical papers listed in Parrott (14,49,54). All these factors lead to a number of interesting questions for future investigation; more specifically, how are these factors related to the acute and chronic psychobiological deficits caused by MDMA.

One of the key concepts behind MDMA research is the notion of 'serotonergic neurotoxicity, which was originally based on extensive animal research (50,57,58; many others). The human findings on this influential concept were the focus for a recent review (49). In the latter paper, it was noted that many neuroimaging studies had found reduced levels of the serotonin transporter (SERT), with significant deficits found across the whole of the cerebral cortex (e.g. 59-62). In terms of functional deficits, lower levels of SERT were correlated with greater neurocognitive impairments (60). Many other areas of psychobiological deficit have also been empirically revealed; they include - changes in sleep architecture, sleep apnoea due to reduced serotonergic control of breathing, subjective complaints of impaired sleep, impaired problem solving, reduced social intelligence, reduced everyday task performance, physical tremor, deficits in the visual processing, altered patterns of brain activity, increased pain perception, reduced immunocompetence, heightened psychiatric distress, and many other problems. There are numerous empirical studies describing these deficits (e.g.63-74; many others). For more detailed coverage of the many relevant empirical studies, see the following reviews (12,14,43-45,49). Another key question is whether these psychobiological deficits recover following drug cessation; the limited data from some early studies was outlined in Parrott (12). More recently, Taurah et al (75) assessed over 100 former users, and compared them to current users, and several non-user control groups. They found that following cessation for an average of four years, functional recovery on the test battery was minimal, with former MDMA users remaining just as impaired as current MDMA users. This suggests that the psychobiological damage caused by MDMA may be relatively permanent. This comprises another key area for future research.

The recreational use of Ecstasy/MDMA by pregnant mothers, has also been shown to lead to significant psychomotor impairments in the emergent children. This has been described in a series of reports, covering the developmental abilities of the children at different ages: 4 months, 12 months and 24 months (76-78). This prospective study followed an earlier medical report, where congenital defects and cardiac abnormalities

were found in mothers who had used MDMA recreationally during their pregnancy (79). Indeed in the DAISY study, one of the 12 children born to the heavier MDMA-using mothers had a rare congenital defect, while there was also significant gender bias in birth outcomes, which was not apparent in the polydrug control group. Further studies of mothers are obviously required. Drug usage by fathers is another important research issue, and it may be a factor of potential interest for sperm donation clinics.

Mephedrone (m-cat) compared to MDMA (Ecstasy)

Mephedrone or meth-cathinone (m-cat) is a member of the cathinone class, with psychobiological effects which are more intense than those generated by cathinone derived from chewing leaves of the Khat plant (80-83). The stronger effects of mephedrone can make its effects similar to those of MDMA in some ways, although different in others. Hence mephedrone and MDMA can lead to positive feelings of euphoria and emotional closeness, while they are typically followed by more negative feelings of tiredness or depression in the post-drug recovery period. This pattern is similar to that found with Khat derived cathinone, and indeed with all other recreational stimulant drugs (39,80-83). The recent history of mephedrone, and how it has become an illicit recreational drug during the past 10 years, has been outlined in the following articles (84-86). However empirical research on mephedrone compares with MDMA is currently very limited (87,88). So that while there has been some debate over their similarities and dissimilarities, there is an urgent need for more empirical data, especially on functional effects.

In order to address this issue, we recently undertook one comparison study of recreational mephedrone and MDMA, and another focused solely on mephedrone. In Jones et al (3) 152 Ecstasy/MDMA polydrug users, and 83 mephedrone/m-cat polydrug users, were recruited through the Internet. They were asked about the average amount of drug taken per session, maximum usage per session, and subjective effects across a range of questions. The incidence of many of the subjective effects was similar for both drugs, with similar levels of positive moods following acute self-administration. However mephedrone users reported more severe recovery issues in the days following usage, along with more problems with sleep, anger and anxiety. It should be noted that these problems were also noted by the Ecstasy/MDMA users,

confirming previous reports of adverse acute effects and mid-week recovery problems (1,2,20,41,42,89). One of the more noticeable differences between these drugs, was the lower acute pharmacodynamic tolerance to mephedrone. With MDMA, repeated self-dosing over a single time period led to weaker subjective effects – due to ‘acute tolerance’. In contrast, mephedrone users reported that repeated self-dosing over a single time period led to continued subjective efficacy – hence they tended to take the drug for longer periods. This more intensive usage may also help to explain why many of the adverse drug effects were comparatively stronger with mephedrone. Our second study (4), assessed psychiatric profiles using the Brief Symptom Inventory, and the personal drug experiences of mephedrone polydrug users. The psychiatric symptom profiles of the mephedrone polydrug users and other polydrug user controls were significantly raised, in comparison with the non-user control group. Many regular mephedrone users also reported that the come-down effects became progressively worse over time, and that they acted as ‘wake-up call’ - for the increasing damage to daily living the drug was causing.

In summary, all the recreational CNS stimulants are psychobiologically damaging. Indeed the damaging effects of Ecstasy/MDMA are broadly similar to those found with established recreational stimulants, such as cocaine, amphetamine and methamphetamine (39). As far as we are currently aware, they are also broadly similar to those found with the NPS drug mephedrone. However more research needs to be conducted into the long-term effects of this novel substance, while similar studies are also needed for Khat-chewing and cathinone (82,83). Hence we need more studies into their neurocognitive, psychomotor, visual, neurohormonal, cardiac, and psychiatric consequences, to see how they compare with the adverse effects of MDMA. Finally, we also need to study the effects of mephedrone and cathinone on foetal development - when taken recreationally during pregnancy.

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