HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2014; **29**: 105–108.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2389

REVIEW ARTICLE

A reconsideration and response to Parrott AC (2013) "Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research"

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Parrott recently published a review of literature on MDMA/ecstasy. This commentary is a response to the content and tenor of his review, which mischaracterizes the literature through misstatement and omission of contrary findings, and fails to address the central controversies in the literature. The review makes several erroneous statements concerning MDMA-assisted psychotherapy, such as incorrect statements about research design and other statements that are baseless or contradicted by the literature. Though it critiques an attempt by other authors to characterize the risks of MDMA, the review fails to produce a competing model of risk assessment, and does not discuss potential benefits. Parrott does not represent an even-handed review of the literature, but instead recites dated misconceptions about neurotoxicity concerns involving the recreational drug ecstasy, which do not relate directly to the use of pure MDMA in a therapeutic setting. Unchallenged, Parrott's report may deter researchers from further investigating an innovative treatment that in early clinical trials has demonstrated lasting benefits for people with chronic, treatment-resistant post-traumatic stress disorder. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—MDMA; ecstasy; psychotherapy; risk-benefit; PTSD

Parrott's paper, "Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research" (Parrott, 2013), concludes that the "damaging effects of ecstasy/MDMA are far more widespread than was realized a few years ago". Our examination of the literature indicates that this view is erroneous, particularly with respect to MDMA-assisted psychotherapy.

MISCHARACTERIZATION OF THE RESEARCH

Parrott claims that there are "new neuropsychobiological deficits still emerging". However, the chart provided (p. 290) does not present any findings unreported from 5 years ago nor does he address confounds shared by nearly all these studies, including the difficulty of matching ecstasy users with appropriate controls and using retrospective over prospective studies (Cole and Sumnall, 2003; Gouzoulis-Mayfrank and Daumann, 2006).

Parrott does not provide information on the strategies used to identify the findings he reviews, and the review does not attempt to separate findings from preclinical research, clinical trials, naturalistic studies, and retrospective between group comparisons, treating them as equally relevant. Furthermore, Parrott seems to assert that the risks of MDMA-assisted psychotherapy should rest upon findings from retrospective studies of people who use illicit, impure ecstasy in unsupervised settings.

Parrott's review frequently exaggerates, misrepresents, or omits research findings. He suggests that the main conclusions of a comprehensive review of the literature (Rogers *et al*., 2009), "was that memory deficits in abstinent ecstasy users were statistically significant in comparison with those in both non-user control groups and polydrug user controls". He omits Rogers *et al*.'s conclusion that the literature was "relatively low quality" and the clinical significance of the memory impairment they detected was liable to be small. In another instance, the review mischaracterizes the findings from a National Institute on Drug Abuse funded study by Halpern and colleagues in a sample of people reporting the use of ecstasy but with

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Received 18 October 2013
Accepted 17 December 2013

little polydrug use (Halpern *et al*., 2011b). Halpern *et al*. reported only a single significant difference between ecstasy users and controls, and no significant differences between heavy and moderate users. In contrast, Parrott claims that heavy users performed worse than moderate users on four measures without stating that these differences were not statistically significant. Halpern interpreted the differences he detected to preexisting differences in self-regulation or to chance, yet Parrott attributes the differences to ecstasy use (Halpern *et al*., 2011a; Parrott, 2011).

When addressing MDMA neurochemistry, Parrott refers to the Biezonski and Meyer review while failing to mention that Biezonski and Meyer do not believe the evidence supports serotonergic neurotoxicity. Parrott's review never directly addresses the controversy surrounding the use of interspecies scaling in preclinical research (Baumann *et al*., 2007). In reference to long-term effects on sleep, a comparison reporting sleep interruption and respiratory disruptions described as sleep apnea (McCann *et al*., 2009), Parrott fails to mention that these results are not confirmed in at least two other studies, one of them of equal or superior design (Carhart-Harris *et al*., 2009; Randall *et al*., 2009) and he ignores the potential significance of smoking, polysubstance use, and male gender in producing relatively high levels of respiratory disruption in both ecstasy using and control groups (Al Lawati *et al*., 2009; Lin *et al*., 2012).

Parrott devotes a section of the review to apoptosis, implying that the findings refer to cell death in human brain cells. Yet to date, publications only report findings in rat brain cells and human liver cells after exposure to high levels of MDMA unlikely to occur after a human equivalent dose of the drug (Jimenez *et al*., 2004; Montiel-Duarte *et al*., 2004; Capela *et al*., 2006; Cadet *et al*., 2007; Upreti *et al*., 2011).

MISSTATEMENTS CONCERNING MDMA-ASSISTED PSYCHOTHERAPY

Parrott's lack of understanding of the clinical issues pertaining to MDMA-assisted psychotherapy is substantial. After noting that MDMA-assisted psychotherapy involves only a few drug-assisted sessions, he states that "this does not fit with current models of pharmacotherapy" such as antidepressants or antipsychotics. He fails to appreciate that MDMA-assisted psychotherapy represents a novel approach to the treatment of post-traumatic stress disorder (PTSD) with the advantage of not requiring daily administration of any drug, avoiding the side effects that daily drug administration can produce. Parrott's statement misses the point.

Parrott states that the psychotherapeutic element may be "more important" than the MDMA-facilitated sessions. However, prior to enrollment, participants in two recent MDMA- assisted psychotherapy studies received at least one form of psychotherapy without reduction in symptoms prior to receiving MDMA-assisted psychotherapy (Mithoefer *et al*., 2011; Oehen *et al*., 2013). Both studies were placebo controlled and double blinded. In the Mithoefer study, both groups received the same manualized psychotherapy. The inactive placebo group received psychotherapy without MDMA and experienced only a 20 point average drop in the Clinician-Administered PTSD Scale (CAPS) compared with a 54 point average drop in the CAPS in the group that received psychotherapy combined with MDMA. Parrott also suggests that the effects of MDMA-assisted therapy were short-lived, yet the published data shows that after a single course of MDMA-assisted psychotherapy participants continued to exhibit reduced PTSD symptoms for an average of over 3.5 years (Mithoefer *et al*., 2013).

In describing Mithoefer and colleagues' results (Mithoefer *et al*., 2011), Parrott states that symptoms were assessed by "the clinician," implying that the people conducting the therapy were also assessing PTSD symptoms. This is incorrect. Mithoefer clearly states that the CAPS was administered by an independent rater not presented during any of the psychotherapy sessions and blind to the dose administered (Mithoefer *et al*., 2011).

Parrott's review mischaracterizes a quote from Greer and Tolbert's report on MDMA-assisted psychotherapy (Greer and Tolbert, 1986), wherein, Parrott quotes only the last sentence of this section: (In full),

> Only 1 subject (#19) experienced post-session psychological difficulties that were disabling, or of more than a few days duration…[He] felt that other events in his life were the causes of his post-session anxiety. A year later, he even felt that his session was probably beneficial. . . . In any case, there is an indication that MDMA may predispose people to a recurrence of previous psychological disabilities (p. 326).

In an unusual paragraph for a scientific journal, Parrott presents two sensationalistic hypothetical situations of what, in his imagination, *might* result from MDMA-assisted psychotherapy. In one, the short-term benefits fade over time leading to addiction to illicit ecstasy and an unsuccessful suicide attempt, and in the other, a veteran is retraumatized by MDMA, causing violent attacks on a stranger. In both

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DOI: 10.1002/hup

cases, these hypothetical patients sue their therapists and the pharmaceutical company marketing MDMA. These surreal fabrications have never even remotely occurred in controlled trials of MDMA-assisted psychotherapy (Mithoefer *et al*., 2011; Mithoefer *et al*., 2013; Oehen *et al*., 2013). Actual objective findings demonstrate safety and lasting improvements with MDMA-assisted psychotherapy with no evidence of any neuropsychological deficits or violence resulting from exposure to MDMA, and a general disinterest in consuming MDMA outside of therapeutic settings.

RECONSIDERATION AND CONCLUSION: BENEFITS AS WELL AS RISKS

Parrott critiques a model for assessing the risks and benefits of recreational drugs (Nutt *et al*., 2007), but does not mention that an independent team of researchers in the Netherlands found that their own model, based on experts rating substances from fact sheets, often matched the ratings generated by Nutt's model (van Amsterdam *et al*., 2010). Parrott fails to offer a competing model for estimating drug harm. By focusing on risk only, he conducts no risk/benefit analysis.

There are no risk-free interventions in use within or outside of medicine; the question is whether these risks are balanced by benefits. Regulatory agencies around the world have approved MDMA/PTSD research protocols on the grounds that the potential benefits outweigh the risks in clinical research settings (Bouso *et al*., 2008; Mithoefer *et al*., 2011; Oehen *et al*., 2013, also see ongoing studies NCT01211405, NCT01958593, NCT01793610, and NCT01689740). More than 850 subjects have participated in regulatory-approved MDMA research without reporting any persisting drug-related harm.

The article by Parrott is a poor representation of the current evidence available to those interested in gaining a balanced picture of MDMA/ecstasy science. Twenty-five years ago, some psychiatrists and researchers expressed concern that the "Ecstasy phenomenon" would result in large-scale psychiatric problems. However, ecstasy never did become the public health scare that was predicted, and concerns around neurotoxicity have remained subclinical. Death rates have remained consistently low and ecstasy-related morbidity does not present in significant numbers to clinics or wards (Rogers *et al*., 2009).

Post-traumatic stress disorder, by contrast, is a disorder with a high rate of treatment resistance by traditional methods and high rates of suicide (Perkonigg *et al*., 2000; Cloitre, 2009; Gradus *et al*., 2010). Novel treatment approaches are urgently needed. MDMA-assisted psychotherapy, like all medical interventions, is not 100% risk free, but it more than adequately satisfies the risk-benefit analysis required to justify its research. To estimate risks based on erroneous, out-dated viewpoints that refer to recreational ecstasy and deny benefits based on hypothetical disaster scenarios demonstrate not only poor scientific methodology, but could also delay those patients who might benefit from such treatments the opportunity for enduring remission from a distressing, disabling, and life-threatening psychiatric disorder.

CONFLICT OF INTEREST

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DOI: 10.1002/hup

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DOI: 10.1002/hup