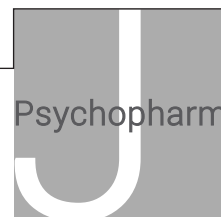


Not too quick on “Debunking the myth of ‘Blue Mondays’”

Jacob Flamelings¹, Floor van der Does², Nancy van Veelen² and Eric Vermetten²



Journal of Psychopharmacology
2022, Vol. 36(8) 1001–1004
© The Author(s) 2022



Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/02698811221100713
journals.sagepub.com/home/jop



Dear Editor,

In their recent article “Debunking the myth of ‘Blue Mondays’: No evidence of affect drop after taking clinical MDMA,” Sessa et al. (2021) reported on results from an open-label study researching the potential use of 3,4-Methylenedioxymethamphetamine (MDMA) in the treatment of alcohol use disorder (AUD). Although we applaud the efforts to ascertain the safety and efficacy of clinical MDMA-assisted therapy for mental health conditions, we have serious concerns that the claims made in this article are not justified by the data. The main conclusion of the authors is that “there is no observable decline in mood after controlled dosing of MDMA in clinical settings,” thereby suggesting “that the ‘comedowns’ previously associated with the substance may be explained by confounds in research relating to the illicit sourcing of the drug and specific environmental setting for recreational consumption.” Although we see the theoretical merit of this claim, and do consider it plausible that sleep disturbances and poor self-care may contribute to the “Blue Monday” effect, we believe that the conclusion that the myth of “Blue Mondays” is debunked is not justified.

Insufficient power and methodology

First and foremost, the title of the article, “Debunking the myth. . .” suggests that there is enough evidence to assume that the “Blue Monday” effect after taking clinical MDMA is a myth, and that it has hereby been debunked. However, the authors must be aware that limited sample size ($N=14$) means that null-findings in this study could easily be a function of a lack of statistical power or a coincidence. Moreover, the problem of limited power is exacerbated by choices made in the statistical analysis of the data. Most patients had multiple MDMA sessions, resulting in a cumulative number of 26 sessions. In order to deal with the interdependency of the data acquired from different sessions in the same participant, the authors have decided to average these POMS scores to result in a single list of 7 POMS scores per patient. However, this means that valuable information is lost as the number of data points in the study is almost halved. This is especially pertinent since an earlier study on the same dataset (see Figure 4 in Sessa et al. (2021)) shown that the course of mood scores differs after the first and second sessions. The correct way to deal with these nested data would have been to use a

hierarchical model. We encourage the authors to perform a reanalysis of their data using the correct statistical procedures, which could enhance the credibility of their article.

The authors stated that “the study was adequately powered to detect improvements in sleep quality as well as mood based on recreational studies with MDMA (Parrott and Lasky, 1998).” Rather than citing a study with a similar N , a power analysis would have been preferable.

Additionally, using this ANOVA, the authors assessed whether a significant difference in mood score occurs in the 7 days after the dosing session. They detected no significant changes, and concluded that there is no evidence of an affect drop after taking clinical MDMA. It would have been informative to know whether this was true for all participants at all respective sessions, as only effects on the group level are reported. Furthermore, the authors posited that the positive mood exhibited by the participants in the 7 days after the session was indicative of an “afterglow” effect. Because there is no control group or baseline measurement of the profile of mood states (POMS), this is a conclusion that cannot be drawn on the basis of these data. As there is nothing to compare these scores with, it cannot be stated that mood was lifted after the session, and this supposed lift in affect was an MDMA effect. It is even possible that mood was more negative after the MDMA session than before—as there is no baseline measurement, we simply do not know. The only fair conclusion that can be drawn is that on the group level, no significant differences could be detected in mood scores of these 14 patients in the 7 days following MDMA dosing sessions.

Lastly, in their discussion, the authors fail to cite the studies from Liechti et al. (2001) and Vizeli and Liechti (2017), which do find evidence for a mood drop in the days following clinical MDMA intake, thereby presenting an unrepresentative view of the current literature.

¹Leiden University, Leiden, Zuid-Holland, The Netherlands

²Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands

Corresponding author:

Eric Vermetten, Leiden University Medical Center, Albinusdreef 2, Leiden, Zuid-Holland 2300 RC, The Netherlands.

Email: E.Vermetten@lumc.nl

Lack of evidence of a causal role of MDMA in improved sleep quality

The authors reported that compared to baseline, patients' quality of sleep improved at the 3 months and 6 months follow-up. We have two concerns about this analysis. First, the lack of a control group means these findings cannot be attributed to the effects of MDMA, and could also be caused by non-specific effects of therapy. Second, in the introduction of the article, the authors did not explain why they measured sleep quality months after MDMA administration. The authors' only mention of sleep quality in the introduction is their hypothesis that the "Blue Monday" effect may be partially due to a lack of sleep, exhaustion, and interactions with other psychoactive drugs, typical for recreational use of MDMA. We, therefore, are left to wonder why sleep quality as measured by the Pittsburg Sleep Quality Index 3 and 6 months after the sessions were reported, even though sleep quality was also measured during the 7 days after MDMA administration using the Leeds Evaluation Questionnaire. In the context of this article, it would make more sense to report on the latter sleep scores.

Social desirability bias in reporting cravings and use of "illicit" MDMA

The authors reported that no participants reported to have "taken illicit MDMA or Ecstasy" nor "had any desire to take illicit MDMA or Ecstasy." We wonder if the authors have considered that the use of the word "illicit" may have implied to the participants that this was an undesirable outcome, thereby increasing the likelihood of a socially desirable "No" response.

Ambiguity in reporting of anecdotal responses

In the qualitative section of this article, the authors decided to only include "all responses that were judged to be clear and unambiguous." We have several questions about this decision. For instance, how did the authors decide what responses were "clear and unambiguous"? Were there multiple raters, and can the authors report inter-rater reliability? These questions also apply to the "list of representative questions and responses" included in Table 3. What does representative mean in this case, and how was representativeness assessed? Additionally, it is possible that rates of unclear and ambiguous responses change following MDMA sessions. Therefore, if these responses are thrown out, valuable information may be lost. Although we find the quotes in Table 3 inspiring to read, they would be more informative if these issues were cleared up. We would encourage the authors to publish all questions and responses as

Supplementary Material so that the reader can judge the representativeness and ambiguity of the responses themselves.

Failure to correct for multiple comparisons

According to the pre-registration of this study, 23 secondary outcome measures were assessed. We wonder why the authors did not correct for multiple testing, and why they did not justify their decision not to. We expect to see more articles coming from this study, and hope to see this issue addressed.

We agree with the authors that the use of psychedelic-assisted therapy in the treatment of various psychiatric disorders shows great promise. Although public opinion of these compounds is improving, many patients still have concerns. We applaud the authors' effort to ease these concerns, and their attempts to support this with research data. However, we think it does injustice to this newly emerging field to believe that the data used in this study are sufficient to substantiate the claims in the title and conclusion. As the authors are operating in a field that is the object of significant public attention and scrutiny, and which may present a source of renewed hope for patients who did not benefit from currently approved treatments, it is very important that the methodologies and statistical and causal inference presented in scientific articles are sound. "Debunking the myth of 'Blue Mondays'" is a compelling title, but by boldly overstating their case, the authors failed to achieve its premise.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jacob Flaming  <https://orcid.org/0000-0002-1425-1180>

Eric Vermetten  <https://orcid.org/0000-0003-0579-4404>

References

- Liechti ME, Gamma A and Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. *Psychopharmacology* 154: 161–168.
- Sessa B, Aday JS, O'Brien S, et al. (2021) Debunking the myth of 'Blue Mondays': No evidence of affect drop after taking clinical MDMA. *J Psychopharmacol* 36: 360–367.
- Vizeli P and Liechti ME (2017) Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol* 31: 576–588.

Reply to: Not too quick on “Debunking the myth of ‘Blue Mondays’”

Dear Flameling et al.,

Thank you for your kind comments applauding our efforts to ascertain the safety and efficacy of clinical 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for mental health conditions. We agree that this is an important topic. The focus of our article (Sessa et al., 2022) was to highlight the differences between safety and risk issues seen in recreational ecstasy use compared to data emerging from the clinical use of MDMA. Looking at the list of authors of our article, you will see we sought multiple inputs from different disciplines within the fields of clinical MDMA and recreational ecstasy experts to provide an informed and wide-reaching opinion on the issue.

In general, the Blue Mondays’ article has received positive support. But it is certainly the case that the choice of the article’s title (“Debunking the myth of ‘Blue Mondays’”) has fostered some criticism. This is largely based on a misunderstanding on the part of some critics who did not read the article in full—and assumed we were suggesting that subjective reports of affect drop post-ecstasy use do not occur amongst recreational users. Although our message was quite the contrary, the phenomenon of post-ecstasy affect drops is a widely reported experience, and the purpose of the article was to contrast this phenomenon with what we saw in our prospective, clinical MDMA study. Although these nuances are difficult if not impossible to fully capture in an article title, we acknowledge that using less powerful language, such as “Challenging the narrative” rather than “Debunking the myth,” may have led to less confusion among readers and better reflected the level of empirical evidence presented in the article.

We shall address all the points you raised in your letter below:

Insufficient power and methodology

In respect of your comments about power and methodology, as above, we were *not* stating that Blue Mondays do not exist in recreational user populations. Quite the contrary, they do. In respect of power: across 26 clinical MDMA sessions, we did not elicit one single report of acute comedowns. All participants reported no negative disturbance to affect at the end of the day after taking MDMA as the drug wore off. No comedowns. This is a highly significant outcome over 26 separate sessions with clinical MDMA. Although we agree that a power analysis would have been preferable, the study was mandated to use a small sample size given it was an exploratory trial of MDMA therapy for alcohol use disorder (AUD).

Thank you for your suggestion regarding re-analyzing the data using alternative statistical methods. We will take this into consideration. We chose to use ANOVA testing to approximate the methods used in influential recreational MDMA studies that found mood drops post-dosing (e.g., Parrott and Lasky, 1998, which at time of writing had >450 citations). Additionally, your suggestion that we include citations to Liechti et al. (2001) as well as Vizeli and Liechti (2017) is valuable, and we appreciate you directing us to this work. It is worthy of note, that Vizeli and Liechti (2017), also using ANOVA testing, found “These safety

data do not raise any concerns related to further studies of MDMA as an adjunct to psychotherapy in controlled medical environments,” and that “the risks and benefits of using MDMA in patients with psychiatric disorders need further study.”

Lack of evidence of a causal role of MDMA in improved sleep quality

Regarding your commentary about a lack of a control group to accurately test whether reported improvements in sleep are specifically due to MDMA drug effects or rather may be attributed to the psychotherapy, indeed. As stated, this is an open-label study, so all outcomes must be interpreted as such. Only a double-blind, placebo-controlled RCT could separate active drug effects from treatment-nonspecific effects (see Aday et al., 2022). We are currently planning such a study.

The Pittsburg Sleep Quality Index (PSQI) is well-suited for use in studies where analysis of sleep quality is not the primary outcome, due to its brevity and returning of a single score representing overall sleep quality (Faulkner and Sidey-Gibbons, 2019). The Leeds Sleep Questionnaire (LSQ) was also conducted as part of the Bristol Imperial MDMA in Alcoholism (BIMA) study, however, was not included in this publication as the PSQI was more succinct in its findings, and sleep was not the primary focus. Future publications will consider as of yet unpublished measures where appropriate.

Social desirability bias in reporting cravings and use of “illicit” MDMA

In respect to our question regarding participants’ use of non-clinical/illicit/illegal MDMA/ecstasy, this was a necessary question to include given that the study is exploring safety and tolerability. The question was asked—and where necessary was discussed face to face—openly with participant responders. You state that using the word “illicit” could have implied to the participants that this was an undesirable outcome, thereby increasing the likelihood of a socially desirable “No” response. It is important to clarify that the study team had a positive therapeutic relationship with all the participants, and we have no reason to suspect that participants would have been disingenuous in answering this question. Almost all of the participants had a history of substantial past polydrug use before coming into the study with AUD and had been frank and open about this at screening interviews. Therefore, the likelihood that this sample would consider admission of illicit MDMA to be “socially undesirable” would, in our opinion, be low.

Ambiguity in reporting of anecdotal responses

In this article, we have not attempted to carry out a formal qualitative analysis of participants’ verbatim reports of tolerability of

the study. Rather, we included some participant quotes to provide some human context to the study. Formal qualitative analysis is indeed a complex skill that requires systematic analysis of participant reports; we are explicit in the article that these are a collection of “anecdotal reports,” and nowhere do we claim to have conducted a qualitative analysis. A more-detailed reporting and analysis of all patients’ comments is beyond the scope of the article. However, we agree that qualitative analyses should be increasingly considered when designing clinical trials with psychedelics to identify mechanisms, risks, and benefits that may not be captured by psychometric scales chosen a priori.

Failure to correct for multiple comparisons

This is so far the third article to be published that came out of the full BIMA project. We did indeed take many more outcome measures than have currently been published, and we are planning to submit further articles for publication. We plan an article soon that will explore the therapeutic psychological model employed in the study, which will include results of several unpublished measures, including commentary about participants’ trauma histories and changes in their compassion and empathy throughout the study. Although the criticism regarding failure to correct for multiple comparisons is well-intentioned, there are a number of practical considerations that limit this technique’s use, particularly in small, exploratory studies (Althouse, 2016). Additionally, in this instance, because examining post-acute mood was decided a priori and an important aspect of the study design, it was justifiable to not adjust *p*-values related to mood.

Conclusion

We welcome debate about our interesting findings. We feel our recent Blue Mondays article contributes positively to the field by providing a clear report of the relative lack of adverse effects seen with clinical MDMA administration in contrast with the

widely reported negative anecdotes seen with recreational use (e.g., comedowns and post-ecstasy affect drop). This is especially relevant given the fact that we were studying potentially vulnerable patients with significant mental and physical illness. We appreciate the criticisms about the article’s hard-hitting title, which has certainly resulted in considerable debate. We hope this discourse can ultimately facilitate further widescale discussions about this important topic and lead to a more nuanced understanding of the risks and benefits of MDMA.

Yours Sincerely,

Dr. Ben Sessa
Dr. Jacob S. Aday
Steve O’Brien, BSc
Dr. H. Valerie Curran
Professor Fiona Measham
Dr. Laurie Higbed
Professor David J. Nutt

References

- Aday JS, Heifets BD, Pratscher SD, et al. (2022) Great expectations: Recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology* 239: 1989–2010.
- Althouse AD (2016) Adjust for multiple comparisons? It’s not that simple. *Ann Thorac Surg* 101: 1644–1645.
- Faulkner S and Sidey-Gibbons C (2019) Use of the Pittsburgh sleep quality index in people with schizophrenia spectrum disorders: A mixed methods study. *Front Psychiatry* 10: 284.
- Liechti ME, Gamma A and Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. *Psychopharmacology* 154: 161–168.
- Parrott AC and Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology* 139: 261–268.
- Sessa B, Aday JS, O’Brien S, et al. (2022) Debunking the myth of ‘Blue Mondays’: No evidence of affect drop after taking clinical MDMA. *J Psychopharmacol* 36: 360–367.
- Vizeli P and Liechti ME (2017) Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol* 31: 576–588.