Challenges with benchmarking of MDMA-assisted psychotherapy

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Matters Arising:

Challenges with benchmarking of MDMA-assisted psychotherapy

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Main:

To represent a treatment breakthrough, MDMA-assisted psychotherapy for posttraumatic stress disorder should be evaluated against first-line psychological interventions or for pre-specified patient subgroups that do not improve after such interventions.

Mitchell et al.[1] recently reported short-term results from a phase 3 trial of MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD), concluding that "[c]ompared with current first-line pharmacological and behavioral therapies, MDMA-assisted therapy has the potential to dramatically transform treatment for PTSD and should be expeditiously evaluated for clinical use". PTSD is a chronic and disabling condition and identifying novel beneficial therapies is timely and important. New treatments could prove useful by being more effective for symptoms or other patient-relevant outcomes (e.g., functioning, quality of life), more cost-effective, or more acceptable to patients (e.g., due to less side-effects). Any of these advantages could apply either to patients overall or to circumscribed subgroups, particularly when these include individuals for whom existent therapies do not work well. However, evaluating new treatments on these parameters necessitates comparing them to interventions currently recommended as "first-line". Benchmarking against the best currently available treatments is fundamental particularly for labeling a new treatment as a "breakthrough", a term with powerful connotations for patients, clinicians and regulators. For PTSD, the current best available treatments are represented by psychological interventions, currently considered as first line treatments for the disorder by most major clinical guidelines such as the American Psychological Association[2] and the National Institute for Health and Care Excellence (NICE)[3]. These guidelines recommend a number of trauma-focused psychological treatments (TFPs), including prolonged exposure therapy (PE), cognitive processing therapy (CPT), eye

movement desensitization and reprocessing (EMDR) and trauma-focused cognitive behavioral therapy (TF-CBT).

In terms of comparative effectiveness, Mitchell et al. reported a reduction in PTSD symptoms (standardized mean difference/SMD) of 0.91 (95% CI 0.44-1.37), which they contrast to the modest effects of some pharmacological treatments, like sertraline (SMD=0.51, 95% CI 0.38-0.64) and paroxetine (SMD=0.36, 95% CI 0.28-0.49)[4]. However, first-line interventions like TFPs are significantly more effective than antidepressants, with SMDs versus control of 0.83 (95% CI 0.69-0.97)[4]. A recent network meta-analysis[5] showed even greater effects on PTSD symptoms for several psychological treatments compared to waitlist, including EMDR (SMD=2.07, 95% CrI 1.44-2.70) and TF-CBT (SMD=1.46, 95% CrI 1.05-1.87). Similarly, in another meta-analysis[6], psychological interventions like CBT (SMD= 0.90; 95% CI 0.68-1.11), exposure therapy alone (SMD=1.05; 95% CI 0.58-1.52) and EMDR (SMD=1.26; 95% CI 0.512.01) were superior to usual care in patients with complex PTSD. Thus, these psychological interventions, which attain similar or higher symptom reduction compared to MDMA-assisted psychotherapy, would represent an appropriate comparator for judging comparative effectiveness.

Examination of another clinically relevant outcome, remission or loss of diagnosis, points to a similar picture. Again, for several first-line psychological treatments, rates are higher than the 33% post-treatment remission reported by Mitchell et al. For example, Ehlers et al.[7] reported post-treatment remission rates ranging from approximately 46% to over 70%, depending on mode of assessment, for two versions of cognitive therapy. A meta-analysis[8] of CBT for PTSD reported a mean remission rate of around 53% (95% CI 45%-61%). Furthermore, Resick et al.[9] demonstrated a remarkable maintenance of effects over an

extensive long-term follow-up for both CPT and PE, with only 22.2% and 17.5% respectively of the intent-to-treat sample of female rape survivors still qualifying for a diagnosis.

Once a novel treatment is proven effective, and particularly if deemed a breakthrough, large-scale dissemination is to be expected. Therefore, two additional aspects to consider are adverse effects (AE) and cost-effectiveness. For the first, serious adverse effects associated with MDMA use reported in Mitchell et al. were rare. However, although rare events are difficult to evaluate reliably in phase 3 trials, due to limited sample sizes and lack of long-term follow-up, they can become noticeable when a treatment is widely implemented. Given that the abuse potential and adverse effects of MDMA, even with limited use, are substantial[10], regulators should require comprehensive evidence on safety and rely on more evidence than a single small study to define an adequate post-approval risk management plan.

Regarding the second aspect, though cost-effectiveness of MDMA-assisted psychotherapy was not yet formally evaluated, it is worth underscoring that the amount of therapy involved is greater than for several first-line psychological interventions. The psychotherapy component in the trial consisted of three preparatory 90 minutes sessions, three 8-hours sessions of delivering MDMA-assisted psychotherapy, each followed by three 90 minutes integration sessions. Overall, the psychotherapy exposure was equivalent to 28 90 minutes sessions or 42 60-minutes sessions. In addition, the presences of two therapists were required in all sessions. Conversely, existing first-line psychological treatments for PTSD, discussed previously, usually consist of 8 to 16 sessions of 60 to 90 minutes duration with an individual therapist[2,3] or up to 20 hours of therapy[7], amounting to half or less than required by MDMA-assisted therapy.

Moving forward, a judgement as to whether MDMA-assisted psychotherapy for PTSD represents a true therapeutic breakthrough requires a phase 3 program that incorporates large

pragmatic studies with adequate comparators, like trauma-focused psychological therapies. Alternatively, the therapy could be tested in rigorously pre-specified subgroups of patients that did not respond to adequate courses of first-line treatments, like TFPs. Given the chronic nature of PTSD and its pervasive and durable impact on patients' lives, trials should also assess patient relevant outcomes beside symptoms, like quality of life, and include mid- and long-term follow-ups. Finally, a thorough investigation of any potential safety issues should be carried out on large samples and at over longer timeframes to ensure a reliable evaluation of the balance of benefits and risks.

Author contributions:

JØH and IAC conceptualized the main arguments, and JØH wrote the first draft. All authors contributed substantially to the revisions of the manuscript.

Ethics statement:

The authors declare no financial or non-financial conflict of interests.

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