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## Challenges with benchmarking of MDMA-assisted psychotherapy

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1 Matters Arising:

2 Challenges with benchmarking of MDMA-assisted psychotherapy

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31 Arising from: Mitchell et al. *Nature Medicine* <https://doi.org/10.1038/s41591-021-01336-3>

32 Main:

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

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

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

57 In terms of comparative effectiveness, Mitchell et al. reported a reduction in PTSD  
58 symptoms (standardized mean difference/SMD) of 0.91 (95% CI 0.44-1.37), which they  
59 contrast to the modest effects of some pharmacological treatments, like sertraline (SMD=0.51,  
60 95% CI 0.38-0.64) and paroxetine (SMD=0.36, 95% CI 0.28-0.49)<sup>4</sup>. However, first-line  
61 interventions like TFPs are significantly more effective than antidepressants, with SMDs versus  
62 control of 0.83 (95% CI 0.69-0.97)<sup>4</sup>. A recent network meta-analysis<sup>5</sup> showed even greater  
63 effects on PTSD symptoms for several psychological treatments compared to waitlist,  
64 including EMDR (SMD=2.07, 95% CrI 1.44-2.70) and TF-CBT (SMD=1.46, 95% CrI 1.05-  
65 1.87). Similarly, in another meta-analysis<sup>6</sup>, psychological interventions like CBT (SMD= 0.90;  
66 95% CI 0.68-1.11), exposure therapy alone (SMD=1.05; 95% CI 0.58-1.52) and EMDR  
67 (SMD=1.26; 95% CI 0.51-2.01) were superior to usual care in patients with complex PTSD.  
68 Thus, these psychological interventions, which attain similar or higher symptom reduction  
69 compared to MDMA-assisted psychotherapy, would represent an appropriate comparator for  
70 judging comparative effectiveness.

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

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

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

89         Regarding the second aspect, though cost-effectiveness of MDMA-assisted  
90 psychotherapy was not yet formally evaluated, it is worth underscoring that the amount of  
91 therapy involved is greater than for several first-line psychological interventions. The  
92 psychotherapy component in the trial consisted of three preparatory 90 minutes sessions, three  
93 8-hours sessions of delivering MDMA-assisted psychotherapy, each followed by three 90  
94 minutes integration sessions. Overall, the psychotherapy exposure was equivalent to 28 90  
95 minutes sessions or 42 60-minutes sessions. In addition, the presences of two therapists were  
96 required in all sessions. Conversely, existing first-line psychological treatments for PTSD,  
97 discussed previously, usually consist of 8 to 16 sessions of 60 to 90 minutes duration with an  
98 individual therapist<sup>2,3</sup> or up to 20 hours of therapy<sup>7</sup>, amounting to half or less than required by  
99 MDMA-assisted therapy.

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

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

110 **Author contributions:**

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

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114 **Ethics statement:**

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

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