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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.¹ 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 Association² and the National Institute for Health and Care Excellence (NICE)³.
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)⁴. 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)⁴. A recent network meta-analysis⁵ 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-analysis⁶, 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.⁷
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-analysis⁸ of
76 CBT for PTSD reported a mean remission rate of around 53% (95% CI 45%-61%).
77 Furthermore, Resick et al.⁹ 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 substantial¹⁰,
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^{2,3} or up to 20 hours of therapy⁷, 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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