ISCTM
International Society for CNS Clinical Trials and Methodology

Bias and Blinding in Psychedelic Trials

Christine Moore, PhD
Vice President, Scientific Solutions
Worldwide Clinical Trials

WORLDWIDE
CLINICAL TRIALS

DISCLOSURES

Dr. Moore is a salaried employee of Worldwide Clinical Trials, an international, full-service, contract research organization that specializes in clinical research activities in support of the pharmaceutical industry. Relationships exist with multiple (>100) pharmaceutical companies as part of the company's primary business activity.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

BIAS AND BLINDING GO TOGETHER

- Bias: systematic tendency of any aspect of the design, conduct, analysis, or interpretation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value.
  - Expectancy bias: subjects on active drug might report more favorable outcomes because they expect a benefit
  - Blinding integrity: how successfully blinding to treatment allocation is maintained
- Routine ways we control bias and blinding
  - Randomization
  - Double-blind treatment allocation
  - Include a control group
- How do we assure blinding integrity and lack of expectancy bias in psychedelic trials? Or can we?

ICH HARMONISED TRIPARTITE GUIDELINE

CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS
E10

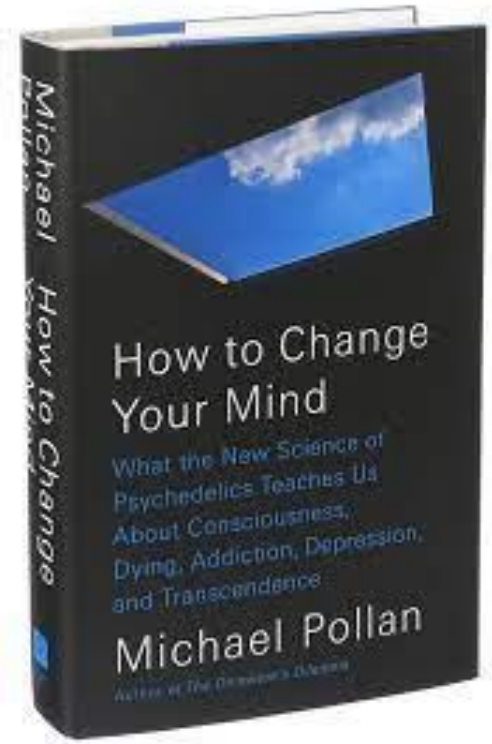
"Blinding is intended to ensure that subjective assessments and decisions are not affected by knowledge of treatment assignment."

"The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed."

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

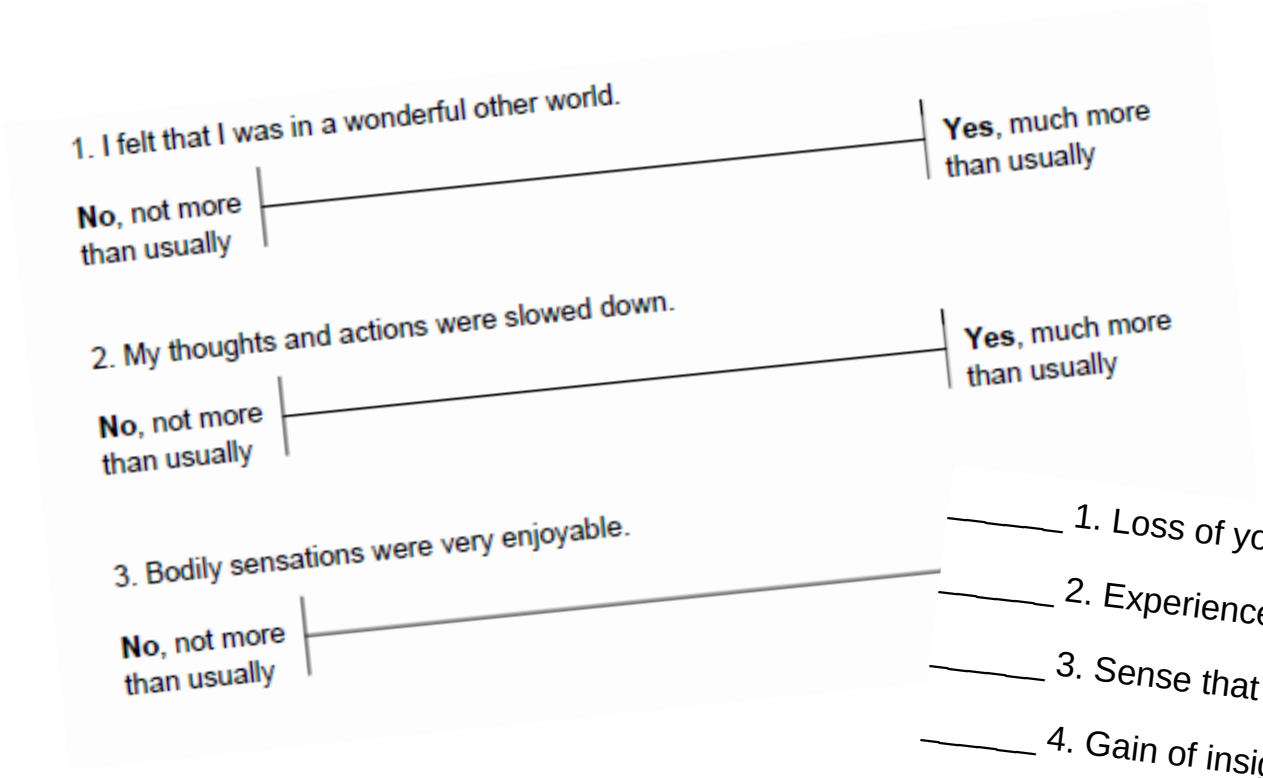
COMPLICATIONS IN PSYCHEDELIC RESEARCH

- Pronounced / salient drug effects (dramatic functional unblinding)
- Drug class induces a state of suggestibility
- Elaborate intervention
  - Treatment model also often involves psychotherapy
  - Setting is important and designed to be “healing”
  - Almost always includes preparatory and integration visits
- Poor understanding of the therapeutic effect
- Endpoints are subjective
- The Pollan effect and highly informed patient population
- Nature of peak / mystical experience questionnaires



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

5D-ASC AND MEQ30 EXAMPLES



_____ 1. Loss of your usual sense of time.

_____ 2. Experience of amazement.

_____ 3. Sense that the experience cannot be described adequately in words.

_____ 4. Gain of insightful knowledge experienced at an intuitive level.

_____ 5. Feeling that you experienced eternity or infinity.

_____ 6. Experience of oneness or unity with objects and/or persons perceived in your surroundings.

_____ 7. Loss of your usual sense of space.

_____ 8. Feelings of tenderness and gentleness.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

HOW OFTEN IS BLINDING INTEGRITY MEASURED?

- Blinding is rarely assessed and when it is, it is often deemed unsuccessful
- Across medicine, < 10% of published trials report assessments of blinding integrity
- Similar in therapeutic areas where outcomes are largely subjective and therefore subject to susceptibility / expectation bias (pain, psychiatry)
  - Earlier reports: ~2 to 7% of RCTs
  - 4.7% to 10% in more recent meta-analyses
    - 16 of 154 studies of antidepressant RCTs from 2000 to 2020 (Lin et al., 2022)
    - 14 of 295 studies up to mid-2020 (Scott et al., 2021)
    - When assessed it is usually with patients, fewer with investigators / raters
    - Blinding assessed both during (6 studies) and at the end of the trial (9 studies)
  - Blind considered successful in 31%; unsuccessful in 19%; 25% reported no conclusion (Scott et al., 2021)
  - Those on active treatment are much more likely to guess correctly
  - Other reports
    - 8 of 94 (8.5%) psychiatric trials reported evidence on successful blinding; 4 were suboptimal (Fergusson et al., 2004)
    - Of 43 studies of ketamine for MDD, 5 measured blinding integrity

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

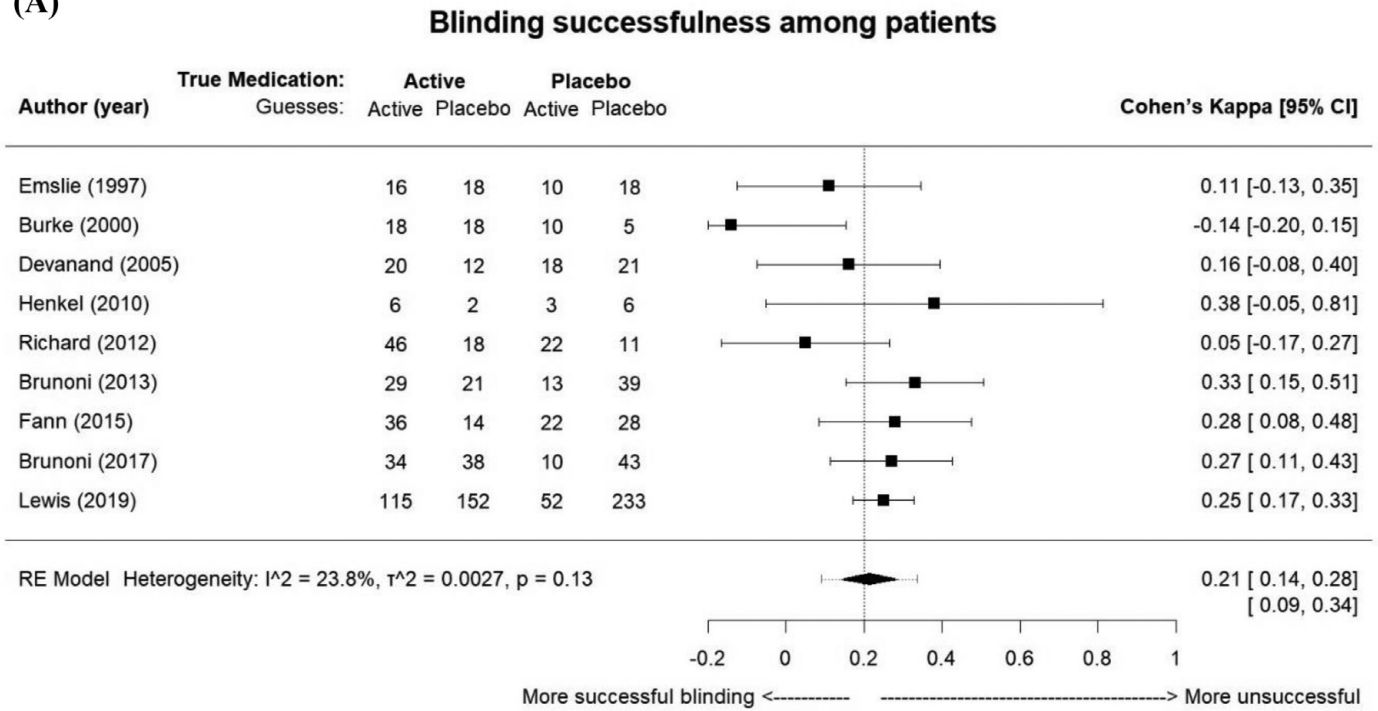
Assessment of blinding in randomized controlled trials of antidepressants for depressive disorders 2000−2020: A systematic review and meta-analysis

*Yi-Hsuan Lin,[a] Ethan Sahker,[a,b] Kiyomi Shinohara,[a] Noboru Horinouchi,[a] Masami Ito,[a] Madoka Lelliott,[a] Andrea Cipriani,[c,d] Anneka Tomlinson,[e] Christopher Baethge,[f] and Toshi A. Furukawa [a]**

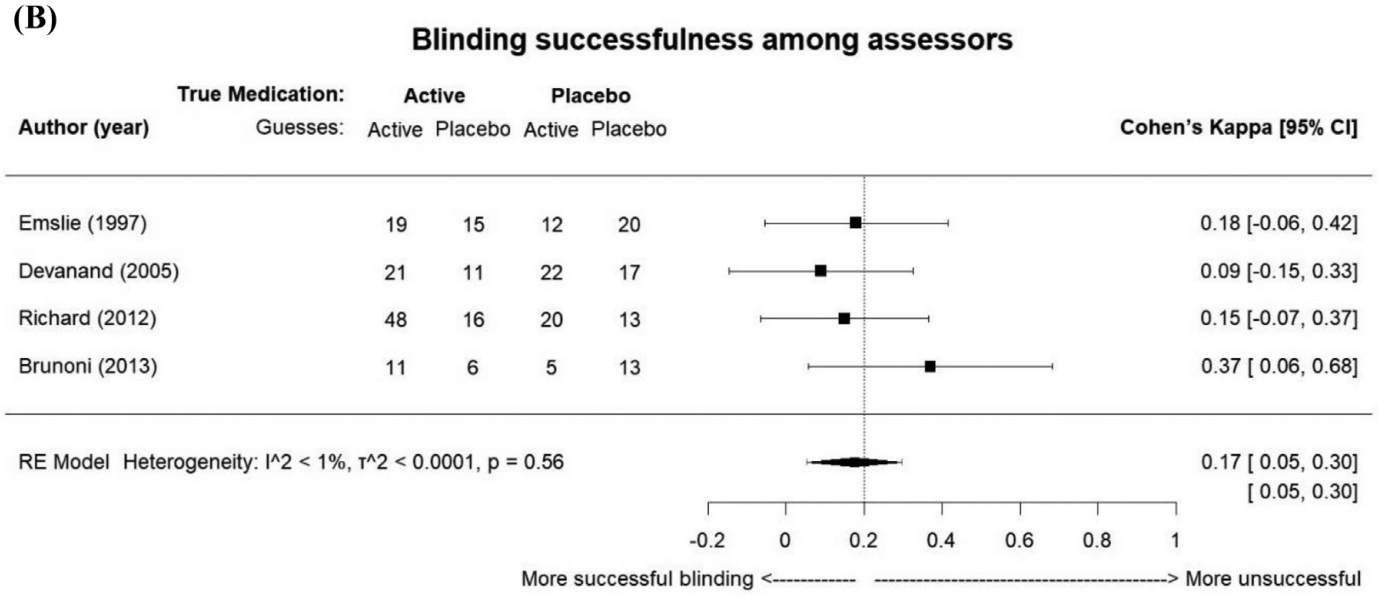
[a]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan
[b]Population Health and Policy Research Unit, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[c]Department of Psychiatry, University of Oxford, Oxford, UK
[d]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK
[e]Manchester Pharmacy School, University of Manchester, Oxford Road, Manchester M13 9PT, UK
[f]Department of Psychiatry and Psychotherapy, University of Cologne Medical School, Cologne, Germany

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

(A)



(B)



Study	Patient Population	Interventions	% correct guess (active) patient	% correct guess (placebo / active control) patient	% correct guess (active) rater	% correct guess (placebo / active control) rater
Rabkin et al., 1986	MDD	Imipramine, phenelzine, placebo	78*	--	87*	--
Margraf et al, 1991	Panic disorder	Alprazolam, imipramine, placebo	83*	--	88*	--
Warner et al, 2001	Bereavement	Diazepam 2 mg, placebo	75	64	--	--
Himle et al, 1999	Anxiety in social phobia	Alcohol, placebo	80	50	--	--
Stoll et al, 1999	Bipolar disorder	Omega-3 fatty acids, placebo	86	63	--	--
Schneier et al., 1998	Social phobia	Moclobemide, placebo	62	45	25	41
Young et al., 1998	PMDD	Sertraline, placebo	100	100	--	--
Fava et al., 2018	MDD	Ketamine 0.1, 0.2, 0.5, 1.0 mg/kg IV, placebo	56, 45, 77, 95 respectively	37	50, 55, 11, 95 respectively	42
Grunebaum et al., 2017	MDD	Ketamine 0.5 mg/kg IV, midazolam	55	55	44	42
Sumner et al., 2020	MDD	Ketamine 0.25 mg/kg/hr IV, remifentanil	86**	--	88**	
Gasser et al., 2014	Anxiety	200 mcg LSD, 20 mcg LSD	100	100	100	67
Palhano-Fontes et al., 2019	TRD	0.35 mg/kg ayahuasca, placebo	100	66	--	--
Ross et al., 2016	Cancer-related anxiety	0.3 mg/kg psilocybin, niacin	--	--	97**	--

*Results not given by treatment group
**Study was a crossover

DATA ON BLINDING INTEGRITY

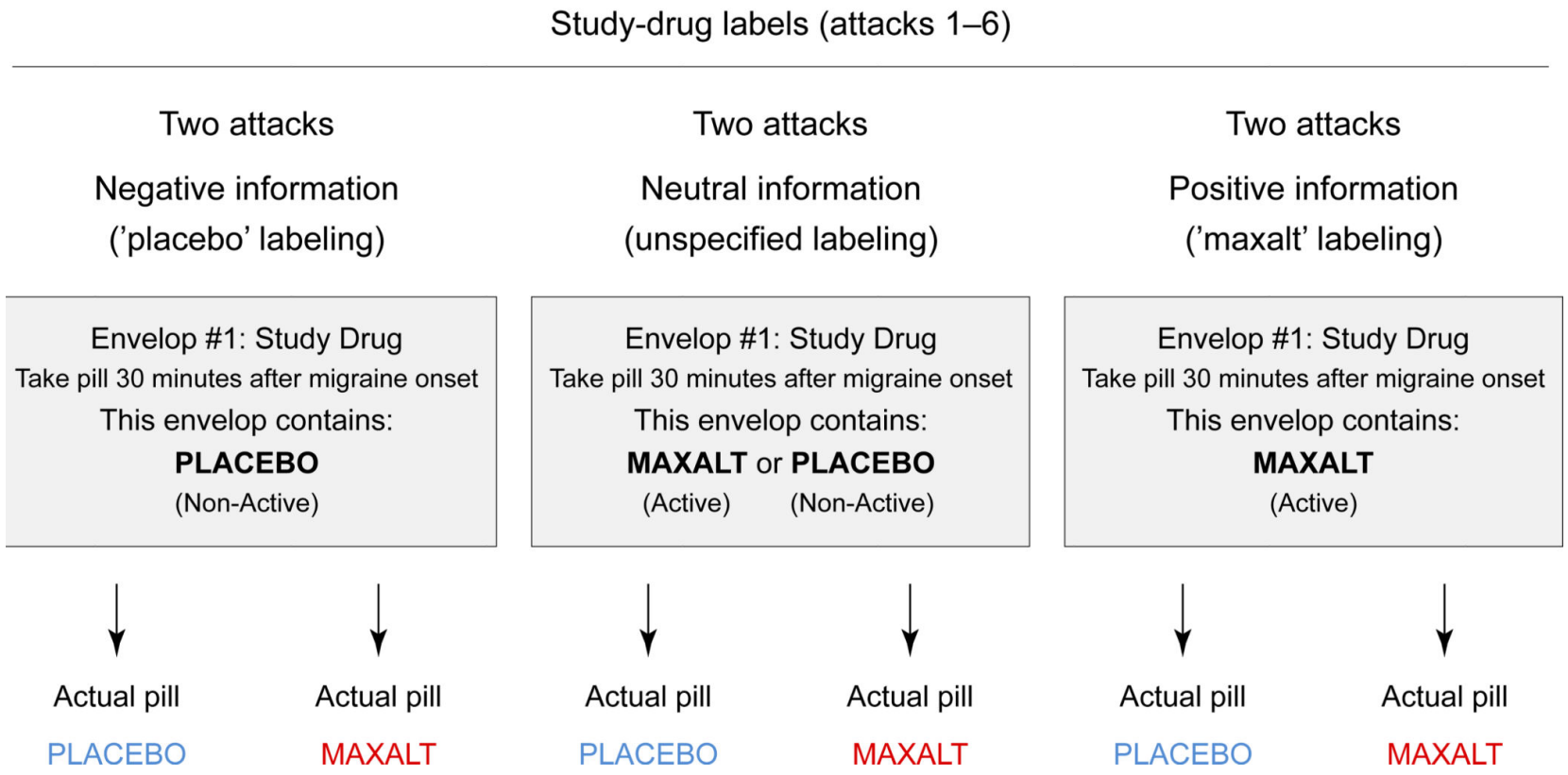
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell[1,2], Michael Bogenschutz[3], Alia Lilienstein[4], Charlotte Harrison[5], Sarah Kleiman[6], Kelly Parker-Guilbert[7], Marcela Ot'alora G.[8,9], Wael Garas[8], Casey Paleos[10], Ingmar Gorman[11], Christopher Nicholas[12], Michael Mithoefer[5,9,13], Shannon Carlin[5,9], Bruce Poulter[8,9], Ann Mithoefer[9], Sylvestre Quevedo[2,14], Gregory Wells[14], Sukhpreet S. Klaire[15], Bessel van der Kolk[16], Keren Tzarfaty[9], Revital Amiaz[17], Ray Worthy[18], Scott Shannon[19], Joshua D. Woolley[2], Cole Marta[20], Yevgeniy Gelfand[21], Emma Hapke[22], Simon Amar[23], Yair Wallach[24], Randall Brown[11], Scott Hamilton[25], Julie B. Wang[5], Allison Coker[1,5], Rebecca Matthews[5], Alberdina de Boer[5], Berra Yazar-Klosinski[4], Amy Emerson[5] and Rick Doblin[4]

- At least 10% inaccurately guessed their treatment arm
  - 7 of 44 participants in the placebo group (15.9%) inaccurately believed that they had received MDMA
  - 2 of 46 participants in the MDMA group (4.3%) inaccurately believed that they had received placebo
- Blinding was also not durable
- Unclear how lack of blinding impacts effect size

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

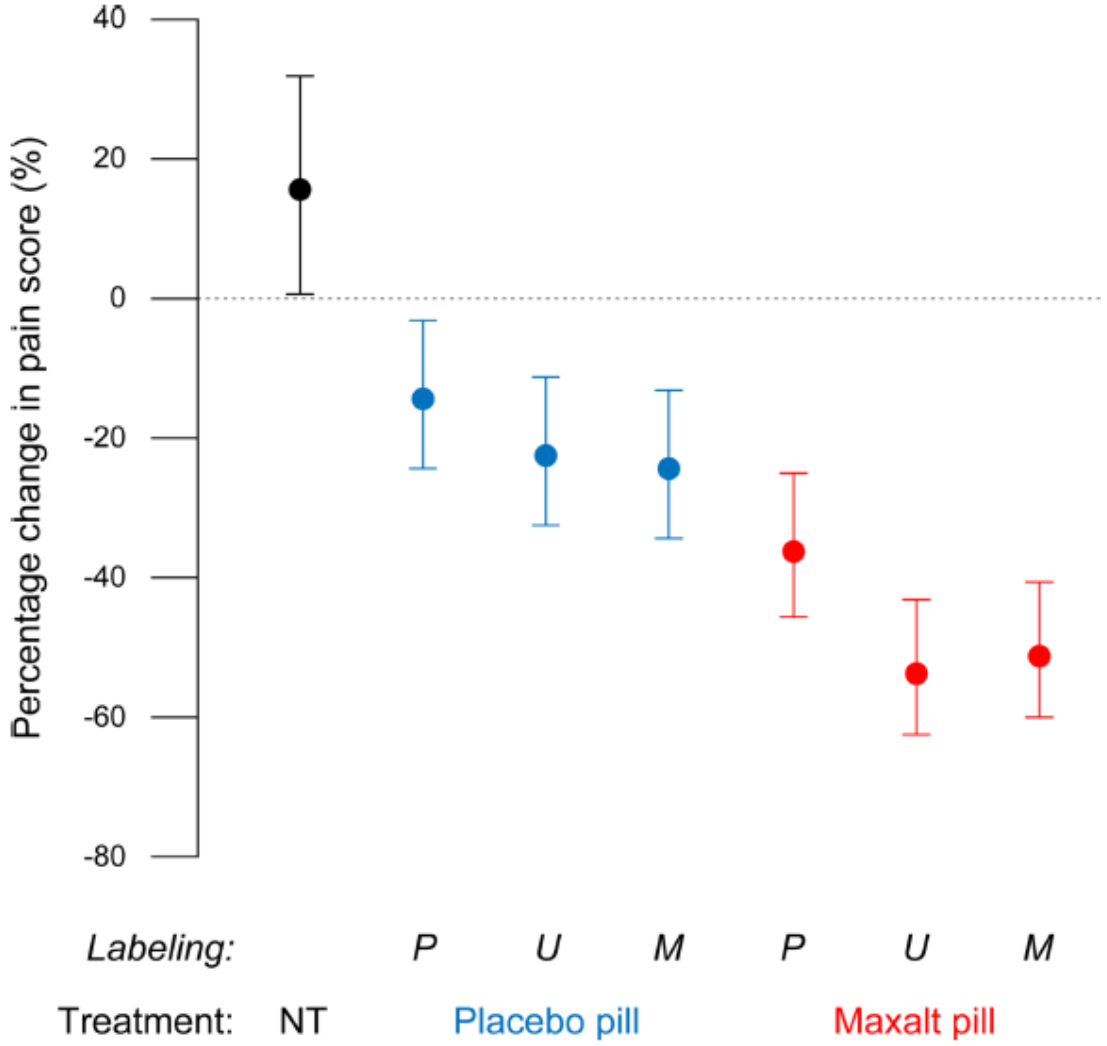
DATA ON EXPECTANCY BIAS



Kam-Hansen et al., 2014

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

DATA ON EXPECTANCY BIAS



"While Maxalt was generally superior to placebo, the placebo effect and to a lesser extent Maxalt efficacy, increased monotonically with treatment labeling as follows: 'Placebo' label < 'Maxalt *or* placebo' label ≤ 'Maxalt' label.

Efficacy of Maxalt mislabeled as placebo was not significantly different from the efficacy of placebo mislabeled as Maxalt.

The placebo effect was significant under each labeling condition relative to no treatment, *amounting in magnitude to >50% of Maxalt effect under the corresponding labeling condition."*

Kam-Hansen et al., 2014

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

DATA ON EXPECTANCY BIAS

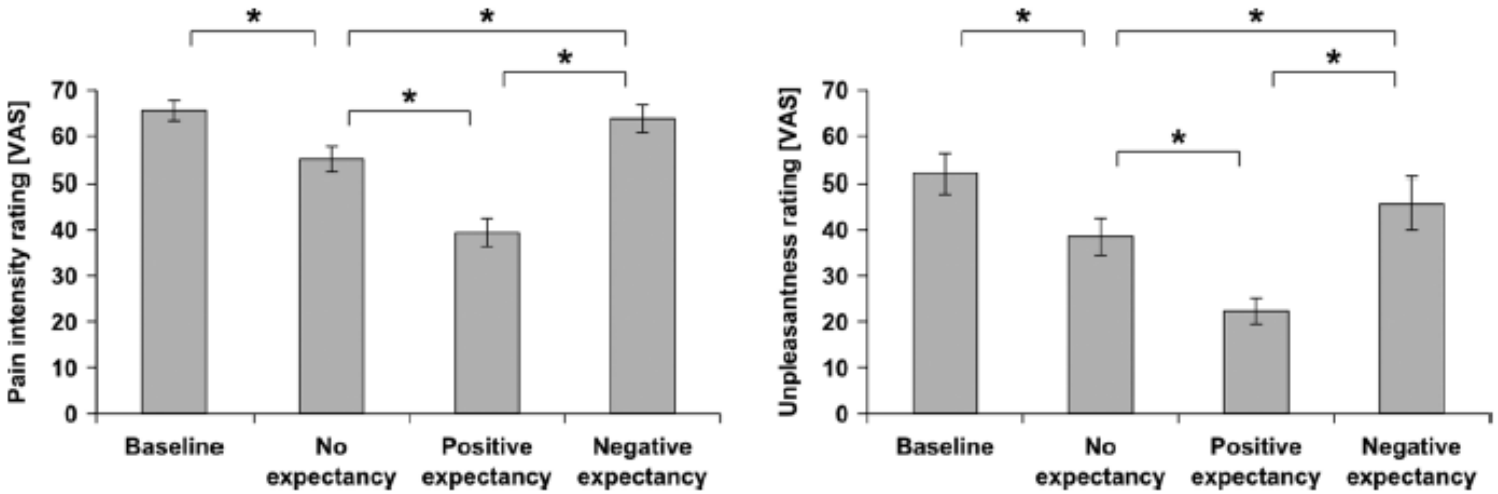


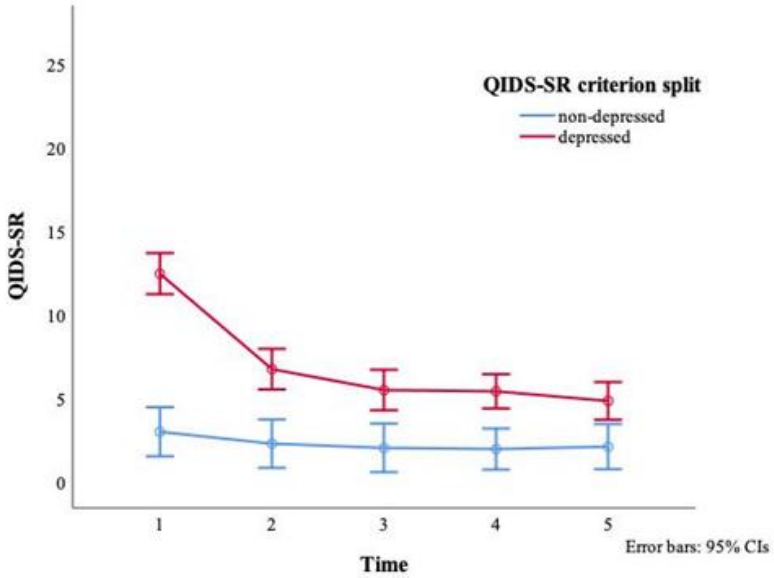
Fig. 1. Behavioral effects of the contextual modulation of opioid analgesia. (Left) Pain intensity ratings obtained on the VAS (0 to 100) for the four experimental runs. (Right) Pain unpleasantness ratings obtained at the end of each of the four experimental runs show the same context-dependent pattern. Error bars indicate SEM. *$P < 0.05$.

Positive treatment expectancy substantially enhanced (doubled) the analgesic benefit of remifentanil. Negative treatment expectancy essentially abolished analgesia. These subjective effects were substantiated by significant changes in brain imaging (Bingel et al., 2011).

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

PSYCHEDELIC STUDY DATA ON EXPECTANCY BIAS

- One macrodosing open-label study of ayahuasca (Weiss et al, 2021)
- Microdosing study
  - Survey in participants planning to start microdosing regimen; expectancy measured by 4 VAS items.
  - Expectations for well-being improvement were significantly associated with change scores in well-being (r=0.275, p=0.007), depressive symptoms (r=−0.263, p=0.009) and anxiety (r=−0.220, p=0.025).
  - “These results indicate that baseline expectations were predictive of mental health change at the study endpoint.”
- Concluded expectancy in microdosing trials may drive treatment effect



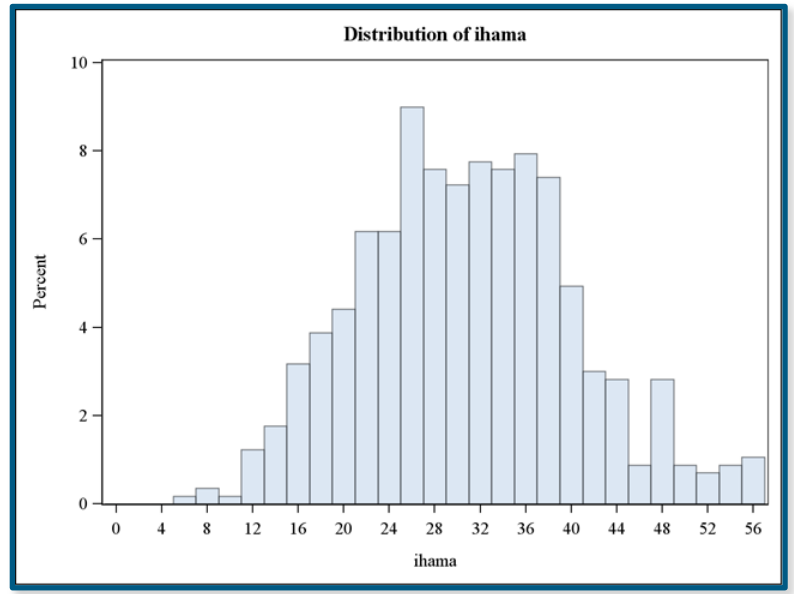
Mean QIDS-SR scores over all time-points are shown for individuals in the depressed range (QIDS–SR > 5) and non-depressed range (QIDS-SR < 5). Error bars represent 95% confidence intervals.

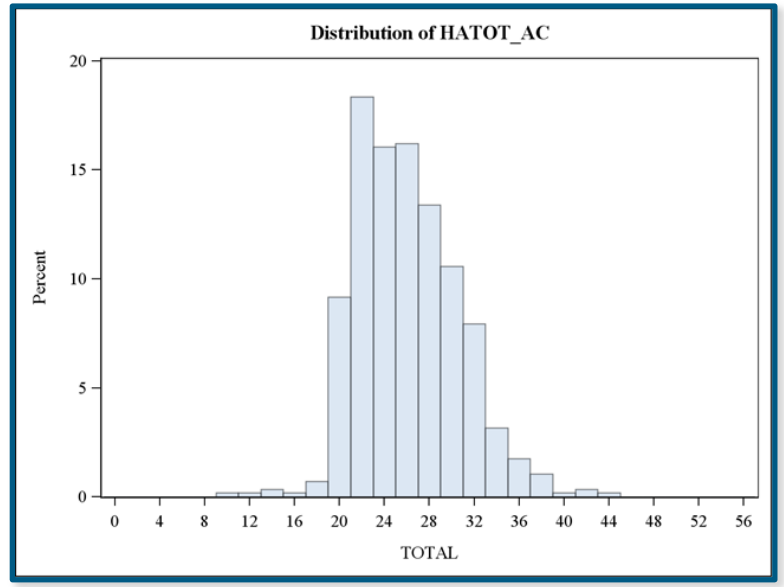
Kaertner et al., 2021.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

WHERE DO WE GO FROM HERE?

- Continued use of double-blind, controlled trials, with careful consideration of the best control
- Strategies commonly used in RCTs across psychiatric indications / drug classes to minimize bias
  - Use one scale for entry purposes and another as the primary outcome
  - Use both self-report and clinician report of symptoms
  - Blind cardinal entry criteria in the protocol
  - Use independent or blinded, centralized raters
- Separate assessment of therapeutic effect from assessment of AEs
- “Placebo” response training programs





ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

WHERE DO WE GO FROM HERE?

- Carefully manage treatment expectancy during the consent process
  - Note change may occur in the absence of a complete mystical experience; clinical outcomes may not be dependent on a psychedelic effect
  - Conversely, a strong psychedelic experience does not guarantee a clinical result.
  - There is significant variability between people—some have strong reactions and others have very mild reactions
  - Psychotherapy by itself is an effective treatment
- In earlier phase studies, recruit psychedelic-naïve patients whenever possible (as well as naïve to the active placebo).

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

WHERE DO WE GO FROM HERE?

- Not commonly used, but worth considering
  - Blind other features of the protocol from participants
    - Mask the number of treatment arms or likelihood of receiving treatment
    - Alternatively consent to receive one of several different compounds
  - May not be approved by ethics committees

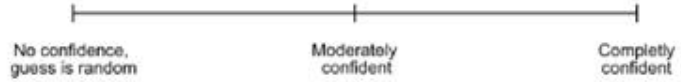
ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

SHOULD WE FORMALLY ASSESS INTEGRITY OF THE BLIND?

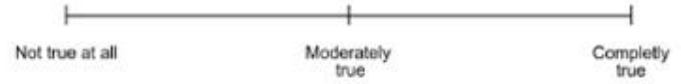
- "..It may be useful for sponsors to ask patients what treatment they think they received and pose similar questions to investigators. An exploratory analysis could consider results in patients who were and who were not unblinded." (FDA Good Review Practice, 2013)
- Historically we have AVOIDED having subjects guess treatment allocation
  - "Testing for 'blindness' may not, and often can't, generate valid answers" (Sackett, 2007)
- There is no accepted standard for assessing blinding integrity or what to do with those data
  - Cohen's kappa
  - Bang or James Blinding Index
  - Use simple VAS for each patient and use as covariate in analyses of individual outcomes
  - Guess of Treatment questionnaire; Correct Guess Rate Curve (CGRC; Szigeti et al., 2022)

1. Please indicate your best guess about the treatment you received:
   - Psilocybin
   - Placebo

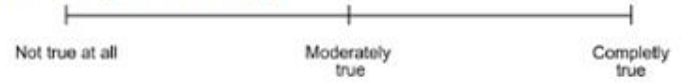
2. Please rate your confident in your guess:



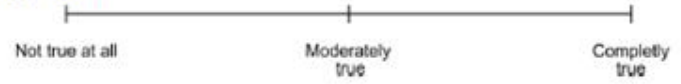
3a. Please rate the following statement: my guess is based on the side effects and/or perceptual drug effects (e.g. muscle tension, visual distortions etc.) that I attribute to receiving an active drug.



4a. Please rate the following statement: my guess is based on health improvements that I attribute to receiving an active drug.



3b. Please rate the following statement: my guess is based on the lack of side effects and/or perceptual drug effects (e.g. muscle tension, visual distortions etc.) that I attribute to receiving placebo.



4b. Please rate the following statement: my guess is based on the lack of health improvements that I attribute to receiving placebo.

5. If factors other than side effects and/or health improvements helped you to formulate your guess, please explain below.
   - [Optional text box response]

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

ASSESS INTEGRITY OF THE BLIND (?)

- When?
  - Relatively soon after dosing but before assessment of outcomes and before subjects begin to perceive potential treatment effects
  - The last questionnaire at the primary endpoint
  - At multiple timepoints to assess the trajectory of unmasking
- Measuring repeatedly may by itself create a response bias
- Who should participants share the guess with?

SHOULD WE ASSESS TREATMENT EXPECTANCY?

- Rarely done and there is no consensus on a process
  - Stanford Expectations of Treatment Scale (SETS)
  - Credibility / Expectancy Questionnaire (CEQ)
  - Simple question “How helpful do you believe the treatment will be for improving you [primary symptom]?”
- Measure in participants, therapists,and raters?
- When to measure? Both at baseline and after dosing?
- Or do we come to terms with the notion that expectancy effects are essentially inextricable from the outcome? (Butler et al., 2022)

Psychopharmacology (2022) 239:3047–3055
https://doi.org/10.1007/s00213-022-06221-6

THEORETICAL AND METHODOLOGICAL PERSPECTIVE

Check for updates

Expectancy in placebo-controlled trials of psychedelics: if so, so what?

Matt Butler[1] · Luke Jelen[1] · James Rucker[1]

Received: 14 March 2022 / Accepted: 23 August 2022 / Published online: 5 September 2022

Abstract
Modern psychedelic research remains in an early phase, and the eventual introduction of psychedelics into clinical practice remains in doubt. In this piece, we discuss the role of blinding and expectancy in psychedelic trials, and place this in a broader historical and contemporary context of blinding in trials across the rest of healthcare. We suggest that premature and uncritical promotion (‘hype’) of psychedelics as medicines is not only misleading, but also directly influences participant expectancy in ongoing psychedelic trials. We argue that although psychedelic trials are likely to significantly overestimate treatment effects by design due to unblinding and expectancy effects, this is not a unique situation. Placebo-controlled RCTs are not a perfect fit for all therapeutics, and problems in blinding should not automatically disqualify medications from licencing decisions. We suggest that simple practical measures may be (and indeed already are) taken in psychedelic trials to partially mitigate the effects of expectancy and unblinding, such as independent raters and active placebos. We briefly suggest other alternative trial methodologies which could be used to bolster RCT results, such as naturalistic studies. We conclude that the results of contemporary placebo-controlled RCTs of psychedelics should neither be dismissed due to imperfections in design, nor should early data be taken as firm evidence of effectiveness.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

SHOULD WE CONSIDER ALTERNATIVE DESIGNS?

- Single dose trials rather than multiple dose trials
- Include an active and inactive control (3 arm trial) to disentangle placebo effects?
- Use of different comparators in different studies in a single NDA
- Designs that have been proposed
  - 2x2 factorial design
  - Using placebo-lead in periods
  - Sequential Parallel Comparison Design (SPCD)
  - Crossover design
  - Offer all active treatment in an OLE, in essence an open-label crossover for those initially on placebo
  - Pretreatment with 5HT2A antagonist (e.g., ketanserin) similar to naltrexone with ketamine
  - Non-conventional designs; e.g., pragmatic studies

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

FUTURE DIRECTIONS

- Consider viability of alternative designs
- If it is determined blinding or expectancy should be formally assessed, need formal recommendations for how to assess and when, with analytic guidelines
- Development of viable active placebo, especially in a psychedelic-experienced population
- Develop objective surrogate endpoints

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

REFERENCES

ICH topic E10 – Choice of control group in clinical trials. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). The European Agency for the Evaluation of Medicinal Products, London, 27 July 2000.

ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. (1999). *Statistics in medicine*, *18*(15), 1905–1942.

Aday, J. S., Heifets, B. D., Pratscher, S. D., Bradley, E., Rosen, R., & Woolley, J. D. (2022). Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology*, *239*(6), 1989–2010.

Muthukumaraswamy, S. D., Forsyth, A., & Lumley, T. (2021). Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert review of clinical pharmacology*, *14*(9), 1133–1152.

Szigeti B, Nutt D, Carhart-Harris R, Erritzoe D. On the fallibility of the placebo control and how to address it: a case study in psychedelic microdosing. PsyArXiv; 2022.

Lin, Y. H., Sahker, E., Shinohara, K., Horinouchi, N., Ito, M., Lelliott, M., Cipriani, A., Tomlinson, A., Baethge, C., & Furukawa, T. A. (2022). Assessment of blinding in randomized controlled trials of antidepressants for depressive disorders 2000-2020: A systematic review and meta-analysis. EClinicalMedicine, 50, 101505.

Scott AJ, Sharpe L, Colagiuri B. A systematic review and meta-analysis of the success of blinding in antidepressant RCTs. Psychiatry Res. 2022 Jan;307:114297.

Fergusson, D., Glass, K. C., Waring, D., & Shapiro, S. (2004). Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. BMJ (Clinical research ed.), 328(7437), 432.

Rabkin, J. G., Markowitz, J. S., Stewart, J., McGrath, P., Harrison, W., Quitkin, F. M., & Klein, D. F. (1986). How blind is blind? Assessment of patient and doctor medication guesses in a placebo-controlled trial of imipramine and phenelzine. Psychiatry research, 19(1), 75–86.

Margraf, J., Ehlers, A., Roth, W. T., Clark, D. B., Sheikh, J., Agras, W. S., & Taylor, C. B. (1991). How "blind" are double-blind studies?. Journal of consulting and clinical psychology, 59(1), 184–187.

Warner, J., Metcalfe, C., & King, M. (2001). Evaluating the use of benzodiazepines following recent bereavement. The British journal of psychiatry : the journal of mental science, 178(1), 36–41.

Himle JA, Abelson JL, Haghightgou H, Hill EM, Nesse RM, Curtis GC. Effect of alcohol on social phobic anxiety. Am J Psychiatry 1999;156:1237-43.

Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56:407-12.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

REFERENCES

Schneier FR, Goetz D, Campeas R, Fallon B, Marshall R, Liebowitz MR. Placebo-controlled trial of moclobemide in social phobia. Br J Psychiatry 1998;172:70-7.

Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomised, double-blind, placebocontrolled crossover trial. J Clin Psychiatry 1998;59:76-80

Fava, M., et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Molecular psychiatry, 2018.

Grunebaum, M.F., et al., Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. American Journal of Psychiatry, 2018. 175(4): p. 327-335.

Sumner, R.L., et al., Ketamine Enhances Visual Sensory Evoked Potential Long-term Potentiation in Patients With Major Depressive Disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2020. 5(1): p. 45-55.

Gasser, P., et al., Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis, 2014. 202(7): p. 513-20.

Palhano-Fontes, F., et al., Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychological Medicine, 2019. 49(4): p. 655-663.

Ross, S., et al., Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of Psychopharmacology, 2016. 30(12): p. 1165-1180.

Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G, M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Klaire, S. S., van der Kolk, B., Tzarfaty, K., … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nature medicine, 27(6), 1025–1033.

Butler, M., Jelen, L., & Rucker, J. (2022). Expectancy in placebo-controlled trials of psychedelics: if so, so what?. Psychopharmacology, 239(10), 3047–3055.

Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Science translational medicine, 6(218), 218ra5.

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Science translational medicine, 3(70), 70ra14.

Weiss, B., Miller, J. D., Carter, N. T., & Keith Campbell, W. (2021). Examining changes in personality following shamanic ceremonial use of ayahuasca. Scientific reports, 11(1), 6653.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

REFERENCES

Kaertner, L. S., Steinborn, M. B., Kettner, H., Spriggs, M. J., Roseman, L., Buchborn, T., Balaet, M., Timmermann, C., Erritzoe, D., & Carhart-Harris, R. L. (2021). Positive expectations predict improved mental-health outcomes linked to psychedelic microdosing. Scientific reports, 11(1), 1941.

van Elk, M., Fejer, G., Lempe, P., Prochazckova, L., Kuchar, M., Hajkova, K., & Marschall, J. (2022). Effects of psilocybin microdosing on awe and aesthetic experiences: a preregistered field and lab-based study. Psychopharmacology, 239(6), 1705–1720.

Good Review Practice: Clinical Review of Investigational New Drug Applications. Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration. December 2013.

David L Sackett, Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't?, International Journal of Epidemiology, Volume 36, Issue 3, June 2007, Pages 664–665.

Rutherford, B.R., et al., A randomized, prospective pilot study of patient expectancy and antidepressant outcome. Psychol Med, 2013. 43(5): p. 975-82

Carhart-Harris, R. L., Wagner, A. C., Agrawal, M., Kettner, H., Rosenbaum, J. F., Gazzaley, 675 A., Nutt, D. J., & Erritzoe, D. (2022). Can pragmatic research, real-world data and digital technologies aid the development of psychedelic medicine? Journal of Psychopharmacology (Oxford, England), 36(1), 6–11.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY