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From Efficacy to Effectiveness: Towards Reliable Evidence-Based Policy for Psychedelic Therapies

Eduardo E. Schenberg, PhD

Instituto Phaneros, Brazil

November, 2024

Disclosures



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“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”

Perspectival Realism



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Winner of the 2023 Lakatos Award: Michela Massimi

PERSPECTIVAL REALISM
MICHELA MASSIMI

OUP author of 'Perspectival Realism'

Winner of the 2023 Lakatos Award

A classical marble statue of a man, likely a philosopher, shown in profile with his hand to his chin in a contemplative pose. The statue is set against a dark background with colorful geometric shapes (orange, pink, blue) at the bottom right.

Does psychedelic therapy work?



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Original Investigation

ONLINE FIRST

August 24, 2022

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial

Michael P. Bogenschutz, MD¹; Stephen Ross, MD¹; Snehal Bhatt, MD²; et al

[Author Affiliations](#) | [Article Information](#)

JAMA Psychiatry. Published online August 24, 2022. doi:10.1001/jamapsychiatry.2022.2096

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

PRIORITY COMMUNICATION | ARTICLES IN PRESS

Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness: A randomized, double-blind, placebo-controlled Phase II study

Friederike Holze · Peter Gasser · Felix Müller · Patrick C. Dolder · Matthias E. Liechti · Show footnotes

Open Access · Published: September 02, 2022 · DOI: <https://doi.org/10.1016/j.biopsych.2022.08.025>

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MDMA-assisted the randomized, double-blind, placebo-controlled phase 3 study

[Jennifer M. Mitchell](#), [Michael Bogenschutz](#), [Kelly Parker-Guilbert](#), [Marcela Ot'alora](#), [Nicholas](#), [Michael Mithoefer](#), [Shannon](#), [Gregory Wells](#), [Sukhpreet S. Claire](#), [Scott Shannon](#), [Joshua D. Woolley](#), [Wallach](#), [Randall Brown](#), [Scott Hami](#), [de Boer](#), [Berra Yazar-Klosinski](#), [Amy](#)

Nature Medicine 27, 1025–1033 (2021)

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MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial

[Jennifer M. Mitchell](#), [Marcela Ot'alora G.](#), [Bessel van der Kolk](#), [Scott Shannon](#), [Michael Bogenschutz](#), [Yevgeniy Gelfand](#), [Casey Paleos](#), [Christopher R. Nicholas](#), [Sylvestre Quevedo](#), [Brooke Balliett](#), [Scott Hamilton](#), [Michael Mithoefer](#), [Sarah Kleiman](#), [Kelly Parker-Guilbert](#), [Keren Tzarfaty](#), [Charlotte Harrison](#), [Alberdina de Boer](#), [Rick Doblin](#), [Berra Yazar-Klosinski](#) & [MAPP2 Study Collaborator Group](#)

Nature Medicine 29, 2473–2480 (2023) | [Cite this article](#)

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2022

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Single-Dose Psilocybin for a Treatment of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBatt M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Je R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.V L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirrow, S. Mistry, T. Mletzko-Crowe, S.R. Offerhaus, V. O'Keane, T. Paleniztek, D. Prinz, M.C. Rademaker, A. van Rier S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywer

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Original Investigation

Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial

Charles L. Raison, MD¹; Gerard Sanacora, MD, PhD²; Joshua Woolley, MD, PhD^{3,4}; et al

[Author Affiliations](#) | [Article Information](#)

JAMA. 2023;330(9):843–853. doi:10.1001/jama.2023.14530

If psychedelic therapy works, how can we know it?



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Original Investigation ONLINE FIRST 🔒
August 24, 2022

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in a Randomized, Double-Blind, Placebo-Controlled Phase II Study

Key Points

Michael P. Bogenschutz **Question** Does psilocybin-assisted treatment improve drinking outcomes in patients with alcohol use disorder relative to outcomes observed with active placebo medication?

Findings In this double-blind randomized clinical trial with 93 participants, the percentage of heavy drinking days during 32 weeks of follow-up was significantly lower in the psilocybin group than in the diphenhydramine group.

[Author Affiliations](#)
JAMA Psychiatry. Published online August 24, 2022. doi:10.1001/jamapsychiatry.2022.2096

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

PRIORITY COMMUNICATION | ARTICLES IN PRESS

Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness A randomized, double-blind, placebo-controlled Phase II study

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Open Access · Published: September 02, 2022 · DOI: <https://doi.org/10.1016/j.biopsych.2022.08.025>

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Article | Open Access | Published: 10 May 2021

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

Jennifer M. Mitchell, Michael Bogenschutz, Alia Lilienstein, Charlotte Harrison, Sarah Kleiman, Kelly Parker-Guilbert, Marcela O'talora G., Wael Garas, Casey Paleos, Ingmar Gorman, Christopher Nicholas, Michael Mithoefer, Shannon Carlin, Bruce Poulter, Ann Mithoefer, Sylvestre Quevedo, Gregory Wells, Sukhpreet S. Klaire, Bessel van der Kolk, Keren Tzarfaty, Revital Amiaz, Ray Worthy, Scott Shannon, Joshua D. Woolley, Cole Marta, Yevgeniy Gelfand, Emma Hapke, Simon Amar, Yair Wallach, Randall Brown, Scott Hamilton, Julie B. Wang, Allison Coker, Rebecca Matthews, Alberdina de Boer, Berra Yazar-Klosinski, Amy Emerson & Rick Doblin [Show fewer authors](#)

Nature Medicine 27, 1025–1033 (2021) | [Cite this article](#)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1912 NOVEMBER 3, 2022

Single-Dose Psilocybin for a Treatment-Resistant Form of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Birnbaum, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirows, S. Mistry, T. Mletzko-Crowe, L.N. S.R. Offerhaus, V. O'Keane, T. Palenčák, D. Printz, M.C. Rademaker, A. van Reemst, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywerna

ABSTRACT

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Original Investigation FREE
August 31, 2023

Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial

Charles L. Raison, MD¹; Gerard Sanacora, MD, PhD²; Joshua Woolley, MD, PhD^{3,4}; et al

[Author Affiliations](#) | [Article Information](#)
JAMA. 2023;330(9):843-853. doi:10.1001/jama.2023.14530

Double-blinded RCT



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Randomization:

Equal distribution of confounders.

Confounder requisites*:

1. Potentially affects the outcome.
2. Is unequally distributed between experimental and control groups.
3. Is unrelated to the experimental intervention.

Double blinding:

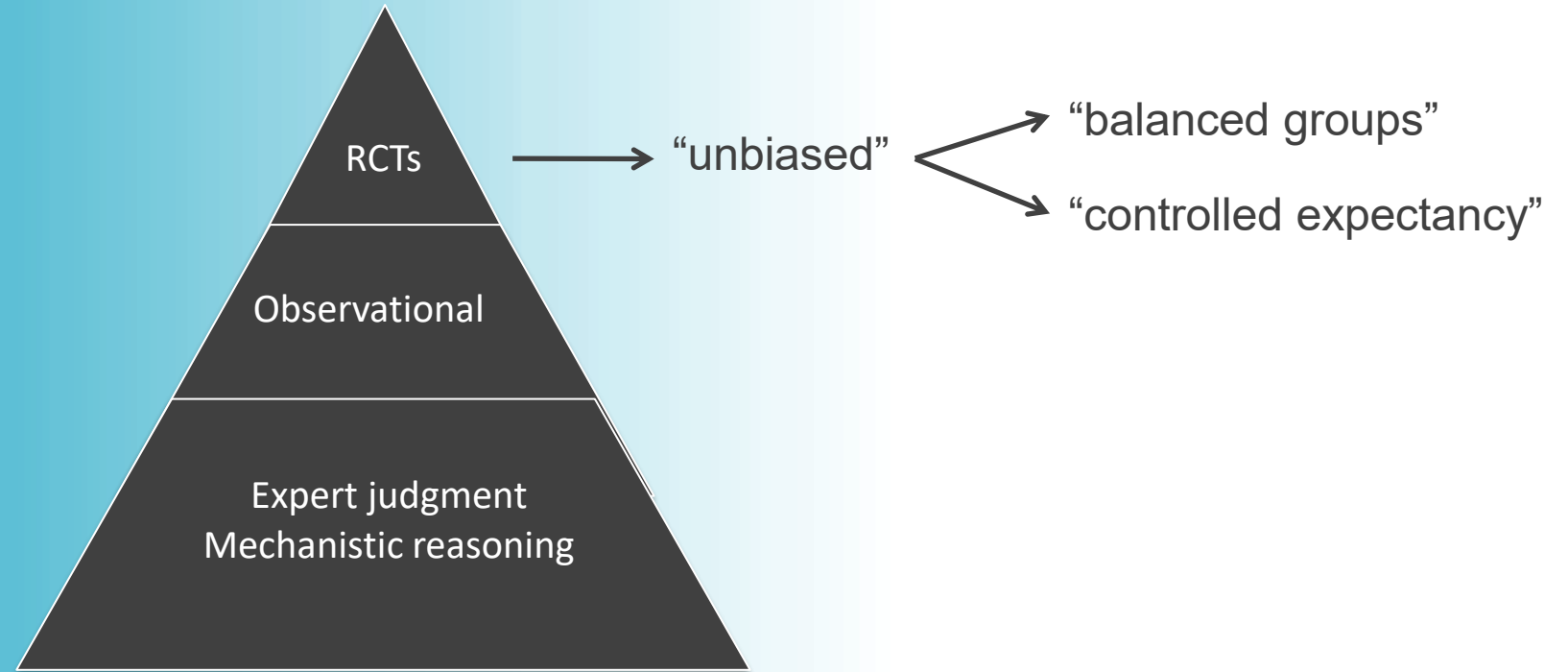
Control for expectancy.

Placebo legitimacy*:

1. Contains all the relevant non-characteristic features of the test-treatment, to the same degree that they are present in the experimental treatment process.
1. Has no additional relevant features over and above the non-characteristic features of the experimental treatment.



EBM's “Hierarchy of evidence”



The philosophy of evidence based-
medicine. Howick J., 2011.

Who is blind in psychedelic research?



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Expert Review of Clinical Pharmacology >
Volume 14, 2021 - Issue 9

Review
Blinding and expectancy confounds in psychedelic randomized controlled trials
Suresh D. Muthukumaraswamy, Anna Forsyth & Thomas Lumley
Pages 1133-1152 | Received 10 Mar 2021, Accepted 19 May 2021, Accepted author version posted online: 26 May 2021, Published online: 26 Aug 2021

Expert opinion: While psychedelic RCTs have generally shown promising results, with large effect sizes reported, we argue that treatment effect sizes in psychedelic RCTs are likely over-estimated due to de-blinding of participants and high levels of response expectancy. We suggest that psychedelic RCTs should routinely measure de-blinding and expectancy. Careful attention should be paid to clinical trial design and the instructions given to participants to allow these confounds to be reduced, estimated and removed from effect size estimates. We urge caution in interpreting effect size estimates from extant psychedelic RCTs.



Review | Published: 01 April 2022
Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials
Jacob S. Aday, Boris D. Heifets, Steven D. Pratscher, Ellen Bradley, Raymond Rosen & Joshua D. Woolley

Psychopharmacology 239, 1989–2010 (2022) | Cite this article
961 Accesses | 1 Citation
Rationale
Psychedelic research continues to garner significant public and scientific interest with a growing number of clinical studies examining a wide range of conditions and disorders. However, expectancy effects and effective condition masking have been raised as critical limitations to the interpretability of the research.

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Matters Arising | Published: 11 October 2021

Caution at psychiatry's psychedelic frontier

Matthew J. Burke & Daniel M. Blumberg

over a placebo control. These are big questions that may take some time to digest and arguably should have been interrogated years ago. Now, we are left in a tough situation: do we continue with status quo measurements and ignore the challenges to validity that these new frontiers create? Or do we begin to transform how we measure efficacy in psychiatry?



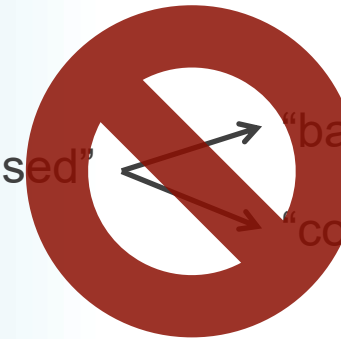
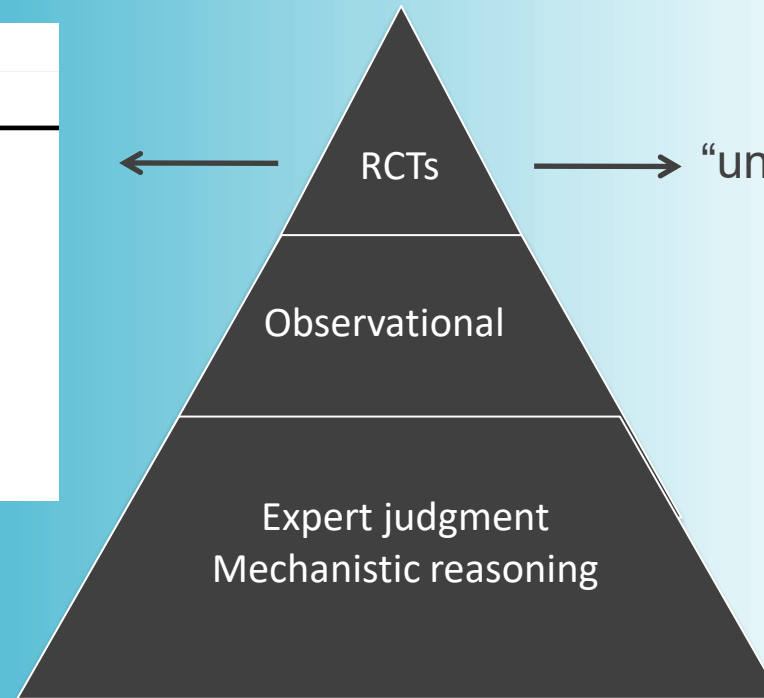
Theoretical and Methodological Perspective | Open Access | Published: 05 September 2022
Expectancy in placebo-controlled trials of psychedelics: if so, so what?

Matt Butler, Luke Jelen & James Rucker

Psychopharmacology (2022) | Cite this article
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.



EBM's “Hierarchy of evidence”



“unbiased”
“balanced groups”
“controlled expectancy”

The philosophy of evidence based-
medicine. Howick J., 2011.

RCTs are not neutral devices



RCT-induced biases

*:

1. Nonconsent bias (different general population);
1. Consent bias (increases side effect expectations);

Blinding induced biases*:

1. Ambivalence, confusion, passivity;
1. Resentful demoralization;
1. Voluntary submission.

*Kaptchuk, 2001



Blinding Assessments in Biomedicine

- Psychedelic studies: **17%** (Nayak et al, 2023).
- 10 Most cited RCTs: **20%** (Kraus, 2018).
- Top 9 journals: General medicine **7%**, Psychiatry **9%** (Fergusson et al, 2004).
- Random 300 trials: **8%** (Bello et al, 2014).
- 1599 trials: **2%** (Hróbjartsson et al, 2007).



RCTs dethroned

BioSocieties (2007), **2**, 11–20 © London School of Economics and Political Science
doi:10.1017/S1745855207005029

Are RCTs the Gold Standard?

Nancy Cartwright

Department of Philosophy, Logic and Scientific Method, London School of Economics, Houghton Street,
London WC2A 2AE, UK

Brit. J. Phil. Sci. **58** (2007), 451–488

Why There's No Cause to Randomize John Worrall

Social Science & Medicine 210 (2018) 2–21



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Understanding and misunderstanding randomized controlled trials

Angus Deaton^{a,b,c,*}, Nancy Cartwright^{d,e}

^a Princeton University, USA

^b National Bureau of Economic Research, USA

^c University of Southern California, USA

^d Durham University, England

^e UC San Diego, USA



Chapter 2 Philosophy of Science Meets Medicine (Again): A Clearer-Sighted View of the Virtues of Blinding and of Tests for Blinding in Clinical Trials

John Worrall

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W. J. Gonzalez (ed.), *Current Trends in Philosophy of Science*, Synthese Library
462, https://doi.org/10.1007/978-3-031-01315-7_2

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Introduction

The parachute is used in recreational, voluntary sector, and military settings to reduce the risk of orthopaedic, head, and soft tissue injury after gravitational challenge, typically in the context of jumping from an aircraft. The perception that parachutes are a successful intervention is based largely on anecdotal evidence. Observational data have shown that their use is associated with morbidity and mortality, due to both failure of the intervention^{1,2} and iatrogenic complications.³ In addition, "natural history" studies of free fall indicate that failure to take or deploy a parachute does not inevitably result in an adverse outcome.⁴ We therefore undertook a systematic review of randomised controlled trials of parachutes.

Methods

Literature search

We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines.⁵ We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.⁶

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Discussion

Evidence based pride and observational prejudice

It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled

Department of Obstetrics and Gynaecology, Cambridge University, Cambridge CB2 2QQ

Gordon C S Smith
professor

Department of Public Health, Greater Glasgow NHS Board, Glasgow G3 8YU

Jill P Pell
consultant

Correspondence to: G C S Smith gcss2@cam.ac.uk

BMJ 2003;327:1459-61



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials



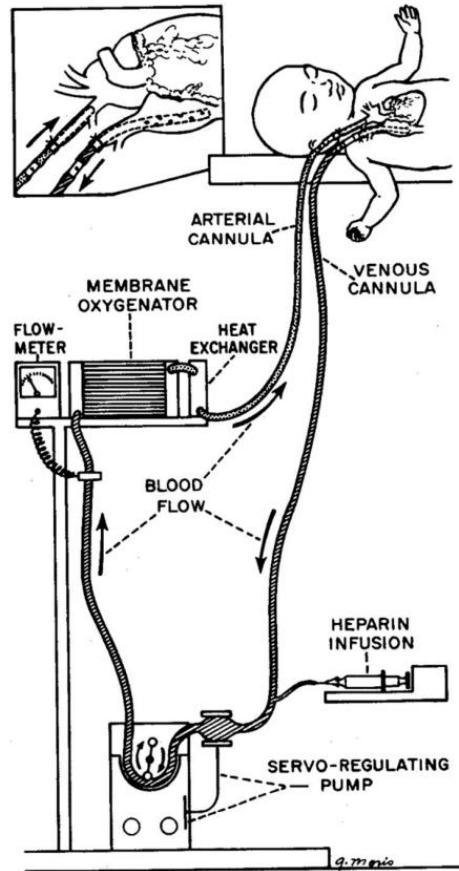


Figure 8. The ECMO mechanism, as depicted by Bartlett et al. (1976).

EBM analysis



OPEN ACCESS

Adapt or die: how the pandemic made the shift from EBM to EBM+ more urgent

Trisha Greenhalgh ,¹ David Fisman,² Danielle J Cane,³
Matthew Oliver ,⁴ Chandini Raina Macintyre⁵

BMJ Evidence-Based Medicine October 2022 | Volume 27 | Number 2 | 523



Two types of psychedelic efficacy:

Chemical Efficacy:

1. Receptor binding
1. Intracellular signaling
2. Neuroplasticity
3. Neuroimaging
4. etc

Self-efficacy:

1. Therapeutic alliance
1. Insights
1. Wellbeing
2. Behaviors
3. Belief changes
4. etc

Hendy, K. *Cult Med Psychiatry* 46, 322–343

RCTs: gold for psychiatry?



Original Investigation

May 9, 2017

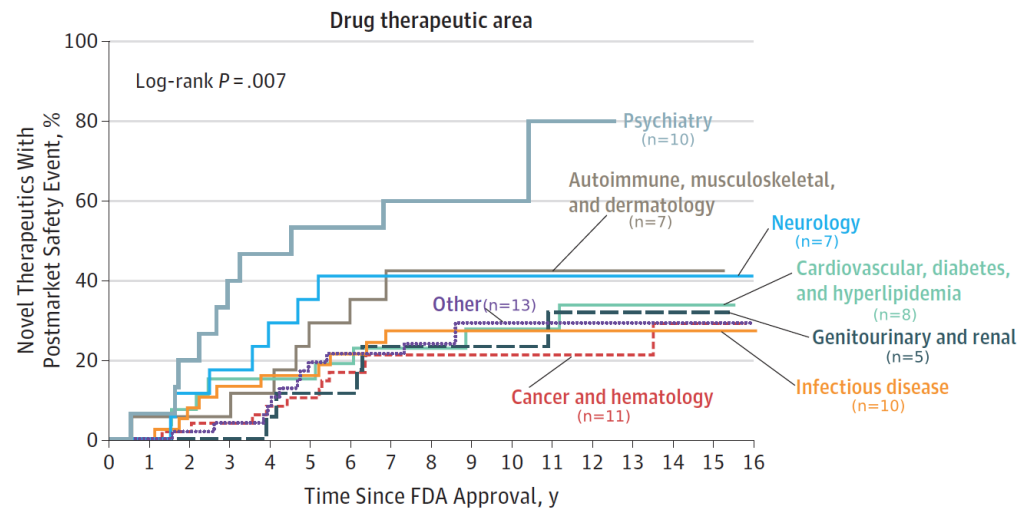
Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD¹; Nilay D. Shah, PhD²; Jenerius A. Aminawung, MD, MPH³; Allison M. Pease, BS⁴; Jean-David Zeitoun, MD, MHPM^{5,6}; Harlan M. Krumholz, MD, SM^{7,8,9,10}; Joseph S. Ross, MD, MHS^{3,8,9,10}

» Author Affiliations | Article Information

JAMA. 2017;317(18):1854-1863. doi:10.1001/jama.2017.5150

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Clinical Development Success Rates 2006-2015

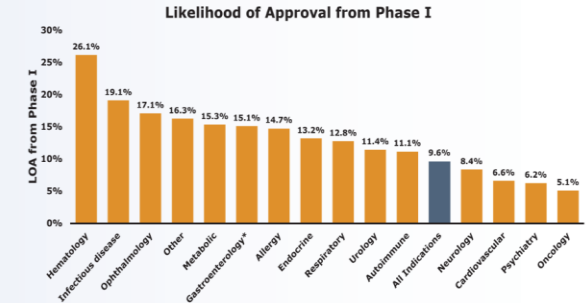


Figure 2a. Chart of LOA from Phase I, displayed highest to lowest by disease area.



Clinical Development Success Rates and Contributing Factors 2011-2020

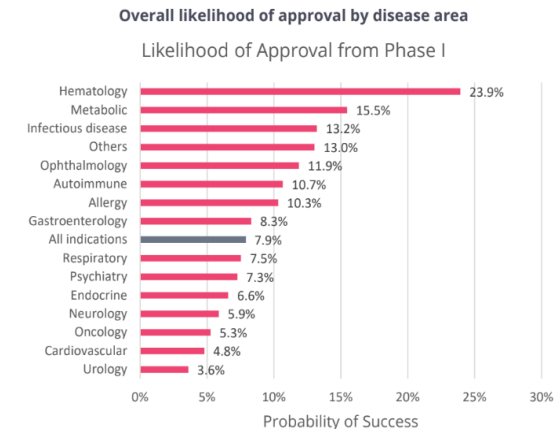


Figure 2a. Chart of LOA from Phase I, displayed highest to lowest by disease area. Source: Biomedtracker® and Pharmapremia®, 2020



Authority of evidence

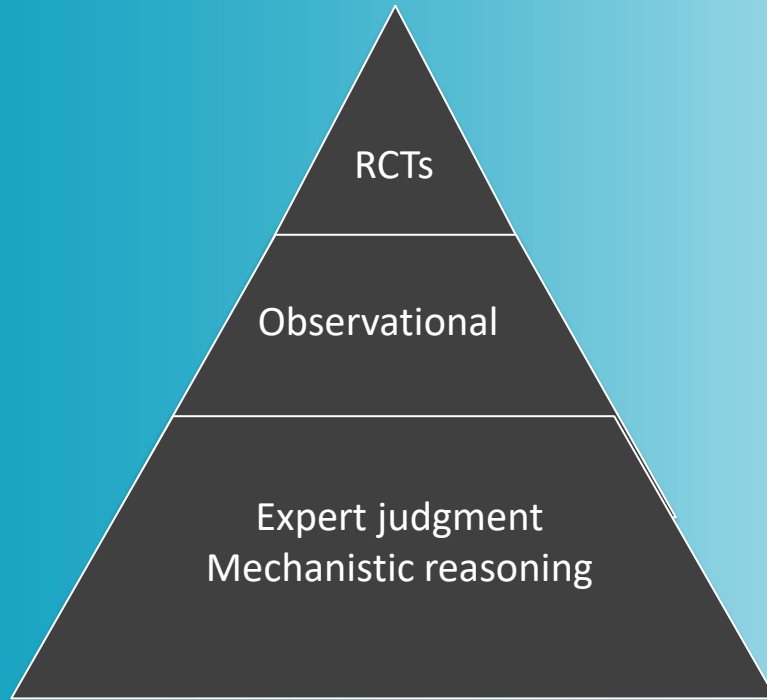
“The authority of evidence that characterizes evidence-based practices does not increase objectivity but rather obscures the subjective elements that inescapably enter all forms of human inquiry.”

Maya Goldenberg, 2005



EBM

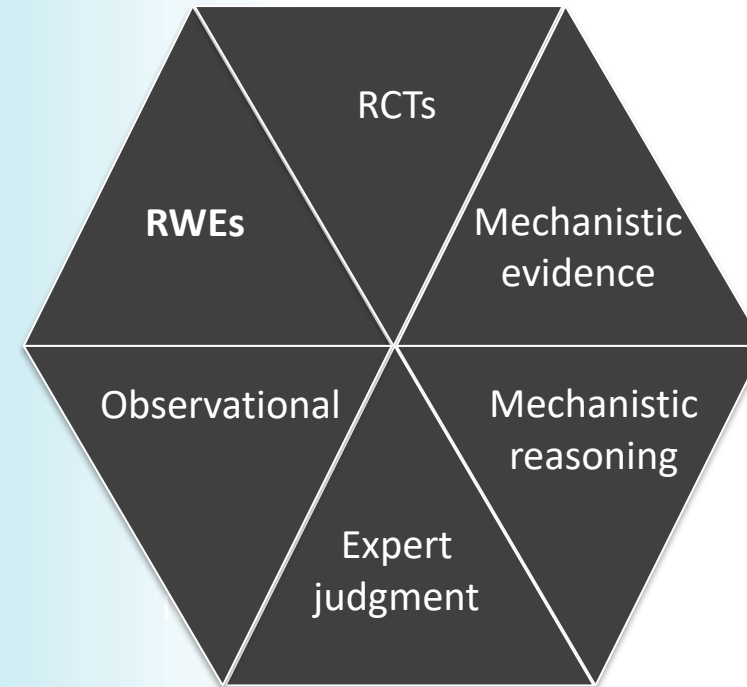
Gold Standard



The philosophy of evidence based-medicine. Howick J., 2011.

EBM +

Evidential Pluralism





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