Can an Antidepressant Change a Life? Evidence, Experience, and Clinical Relevance

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ABSTRACT

The efficacy of antidepressants has been the subject of an intense debate. Much of the evidence-based criticism has focused on the interpretation of average effect sizes derived from clinical trials and meta-analyses. In this context, results frequently described as "clinically non-significant" have fueled skeptical, and at times even nihilistic, views regarding their therapeutic usefulness. However, this way of reading the evidence proves insufficient to account for the complexity of real-world treatment and the processes that sustain recovery beyond the isolated pharmacological effect.

This article proposes a reflection from an integrative psychiatric perspective, aimed at incorporating biostatistical data within the clinical context and the experience that emerges from the encounter between clinician and patient, while questioning the automatic identification between statistical significance and clinical relevance.

It is argued that modest reductions in symptom scales may acquire a decisive value in contexts of intense suffering, where small changes allow the recovery of basic functioning, the sustaining of daily life, or the facilitation of other therapeutic processes. Finally, an integrated reading is proposed that avoids both indiscriminate medicalization and the simplistic rejection of interventions with modest average effects, reaffirming clinical judgment, the therapeutic relationship, and a values-based psychiatry.

Keywords: antidepressants, clinical relevance, clinical judgment, values-based psychiatry, therapeutic relationship.

¿Puede un antidepresivo cambiar una vida? Evidencia, experiencia y relevancia clínica

RESUMEN

La eficacia de los antidepresivos ha sido objeto de un intenso debate. Gran parte de la crítica basada en la evidencia se ha centrado en la interpretación de tamaños de efecto promedio obtenidos en ensayos clínicos y metanálisis. En este contexto, muchos resultados frecuentemente descriptos como "clínicamente no significativos" han alimentado lecturas escépticas o incluso nihilistas sobre su utilidad terapéutica. Sin embargo, esta forma de leer la evidencia resulta insuficiente para dar cuenta de la complejidad del tratamiento real y de los procesos que sostienen una recuperación más allá del efecto farmacológico aislado.

Este artículo propone una reflexión desde una perspectiva integradora en psiquiatría, orientada a incluir los datos bioestadísticos con el contexto clínico y la experiencia que se construye en el encuentro entre

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profesional y paciente, poniendo en cuestión la identificación automática entre significancia estadística y relevancia clínica.
Se argumenta que reducciones modestas en escalas de síntomas pueden adquirir un valor decisivo en contextos de sufrimiento intenso, donde pequeños cambios permiten recuperar funciones básicas, sostener la vida cotidiana o habilitar otros procesos terapéuticos. Finalmente, se propone una lectura integrada que evite tanto la medicalización indiscriminada como el rechazo simplista de intervenciones con efectos promedio modestos, reivindicando el juicio clínico, el vínculo terapéutico y una psiquiatría basada en valores.

Palabras clave: antidepresivos, relevancia clínica, juicio clínico, psiquiatría basada en valores, relación terapéutica.

INTRODUCTION

This article offers a critical reflection on the clinical relevance of antidepressants in light of the contemporary debate surrounding their efficacy. It seeks to integrate quantitative evidence, clinical experience, and the assumptions that shape the clinician's approach to patient suffering. The central question is whether statistical significance can be automatically equated with clinical relevance, particularly when average effect sizes are interpreted as "small" or "not clinically significant."

We can organize the contemporary debate on antidepressant efficacy around three positions. The first, represented by the network meta-analysis by Cipriani et al., published in *The Lancet* in 2018, draws on 522 clinical trials involving more than 116,000 patients and concludes that most of the antidepressants studied are significantly more effective than placebo, with differences in efficacy among individual antidepressants.[1] This position is strongly defended by Goodwin and Nutt, who argue that the number needed to treat (NNT) for selective serotonin reuptake inhibitors (SSRIs) is comparable to that of many drugs used to treat medical conditions and that criticism of antidepressants reflects biases in the debate rather than genuine limitations of the evidence.[2] Hieronymus et al. further support this position, arguing that the threshold for clinical relevance proposed by critics is arbitrarily high and imposes standards that no medical treatment would meet.[3]

The second position, associated primarily with Kirsch,[4,5] Moncrieff,[6,7] and Hengartner,[8,9] maintains that this difference, although statistically significant, is clinically trivial and overestimated because of biases in the research process. This position is further supported by Munkholm et al.'s reanalysis of the original data from Cipriani et al., which questions the quality of the evidence when assessed according to GRADE criteria.[10]

The third position, proposed by Vöhringer and Ghaemi, differentiates according to severity and clinical context, maintaining that antidepressants are clearly effective in moderate and severe depression but probably ineffective in mild depression.[11] The present reflection aligns with this position but seeks to take it one step further.

Three key terms in the literature on antidepressant efficacy, often treated as synonyms, should be clarified. Following the consensus established by Frank et al. in 1991 and revised by the ACNP Task Force in 2006:[12,13] response refers to a ≥50% reduction in symptom severity from baseline; remission, to a virtually asymptomatic state (17-item Hamilton Depression Rating Scale [HAM-D-17] score ≤7) sustained for at least two to three weeks; and recovery, to remission sustained for at least four to six months, long enough for the episode to be considered over. This distinction is relevant because contemporary criticism of antidepressants is often framed in terms of response in short-term trials. When the time horizon is extended to sustained remission or recovery, the figures become even more modest.

The clinically relevant question, then, is what role we assign to medication within the therapeutic process. This issue is related to the classic distinction between efficacy and effectiveness. Efficacy refers to what a drug produces under the controlled conditions of a randomized clinical trial (RCT), where strict patient selection criteria, the exclusion of complex comorbidities, short follow-up, and the standardization of clinical management to a minimum are intended to isolate the drug effect. Effectiveness refers to what that same drug produces in real-world clinical practice, where the patient's life history. These comorbidities would have led to exclusion from a trial; variable adherence and the therapeutic setting also factor into the phenomenon being treated.

Most of the evidence that dominates the debate on antidepressants concerns efficacy. Standardized mean differences (SMDs), NNTs, and differences in HAM-D scores come from trials designed to isolate the pharmacological effect. Effectiveness research also exists and shows that, with longer follow-up and in real-world populations, sustained remission rates are even more modest than those observed in traditional RCTs. The largest pragmatic trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), showed remission rates of approximately 30% with the first SSRI under routine clinical practice conditions, reaching a cumulative rate of 67% after four successive treatment steps. However, relapse rates approached 50 % at

12-month follow-up.[14] These data illustrate the limits of what medication can achieve on its own, both in terms of acute improvement and the sustainability of that improvement over time, and raise the question of which clinical processes accompany pharmacological treatment in cases in which recovery is sustained. Both the efficacy and effectiveness debates focus on the drug's effect in isolation, leaving aside the clinical-setting dimension that this article seeks to address.

Let us therefore shift the discussion to clinical practice, where its meaning ultimately lies. The following scenario is an illustrative construction, although any psychiatrist will recognize it as a common clinical presentation, and is intended to give concrete form to the argument. It is late on a Monday afternoon in the consulting room. Sitting across from us is a patient who, for the past month, has been unable to get out of bed and has been thinking about quitting her job, leaving her partner, and "disappearing." She has a child waiting for her, a boss putting pressure on her, and a burden of shame and exhaustion that no rating scale can fully capture.

After a few weeks of treatment, something begins to shift. She is still tired and continues to have dark moments, but she starts arriving at work on time again, resumes an activity she had abandoned, and can say "no" in situations where she had previously suppressed her own needs. If we had to capture that change in a headline, it would probably be: "She could breathe again." This scenario offers a starting point for examining what gets left out when therapeutic effects are measured exclusively in averages.

Let us now change settings. We are no longer in the consulting room but are analyzing a meta-analysis, surrounded by curves, effect sizes, and standard deviations. There, the same intervention that helped this patient function a little better appears under a different label:

"SMD = 0.3. Small effect. Not clinically significant."

A gap between these two descriptions deserves attention. Criticism of antidepressants is necessary; the evidence has genuine methodological limitations, the placebo effect is substantial, and the medicalization of suffering entails real risks. But if we rely exclusively on certain statistical thresholds, we end up making a claim that sounds absurd in clinical practice: that a tool capable of tipping the balance in the lives of many people "does not work."

Returning to the points raised in the introduction, the argument warrants further emphasis. Scott Alexander Siskind argues that if we applied to all pharmacological treatments the same criteria used to judge antidepressants, many of the drugs we now consider standard of care would be dismissed as "not significant."[15] Goodwin and Nutt have shown that the NNT for antidepressants is comparable to that of many drugs used to treat chronic medical conditions, making it difficult to justify the asymmetry whereby antidepressants are required to meet a higher threshold of efficacy than other pharmacological treatments.[2] The question, then, is what we are measuring –and what we leave out– when we reduce efficacy to a number.

DEVELOPMENT

A Universal Translation—with a Caveat

To compare interventions of different kinds, clinical research relies on a common measure: effect size. This statistical tool quantifies the magnitude of a difference between two groups in relative terms, regardless of the original measurement scale. In antidepressant trials, the most widely used metric is the SMD, which is very similar to Cohen's *d*.[16] The SMD indicates how far the treatment group is from the placebo group, measured in standard deviation units. In 1988, Cohen proposed a convention for interpreting these values:[17]

~0.2: small effect
~0.5: moderate effect
~0.8: large effect

This rule is useful as a reference, but it is just that—a convention. It is not a law of nature, and using it as a rigid threshold for deciding whether something "works" or "does not work" is a major source of misunderstanding.

It is important to clarify from the outset that a small effect size does not automatically imply a lack of clinical relevance. Effect size describes an average difference between groups, whereas clinical significance depends on context, baseline severity, the patient's goals, and the functional impact of the change. An SMD of 0.3 may be irrelevant in a mild condition yet clinically decisive in severe depression accompanied by substantial functional impairment. Confusing statistical magnitude with clinical relevance is one of the most common errors in this debate.

The Modest-Effect Argument

This is the position advanced by Kirsch,[4][5] Moncrieff,[6,7] Hengartner,[8,9] and Munkholm.[10] Most trials assess depression using scales such as the Hamilton Depression Rating Scale (HAM-D), and for many years, organizations such as the UK National Institute for Health and Care Excellence (NICE) traditionally considered a "clinically relevant" difference to require at least 3 points on the HAM-D-17 or an SMD greater than 0.50.[18] The current NICE guideline (NG222, 2022) abandoned this specific threshold and continues to recommend antidepressants as a first-line treatment for moderate and severe depression, recognizing their clinical utility beyond statistical criteria.

Irving Kirsch's meta-analysis of data submitted to the US Food and Drug Administration (FDA) shows that the average difference between antidepressants and placebo is approximately 1.8 to 2 points on the HAM-D, corresponding to an SMD of ~0.30.[4,5] Based on these figures and the NICE threshold, the conclusion seems inevitable and has become a recurring headline: the benefit falls below accepted criteria for clinical significance. Framed in these terms, the conclusion would appear straightforward: antidepressants barely outperform placebo. However, it is worth examining

how well calibrated the tool we use to measure this effect actually is.

DISCUSSION

A study by Leucht et al. did something simple yet revealing: it compared the effect sizes of psychotropic drugs with those of medications used in other medical specialties.[19,20] The findings came as a surprise to many: the average effect of an antidepressant on depressive symptoms is similar to or greater than that of statins for some preventive indications. In Leucht's review, several widely used medical treatments show effect sizes similar to or even smaller than those of antidepressants: statins for cardiovascular prevention have an SMD of approximately 0.15 and aspirin for secondary prevention an SMD of approximately 0.12, whereas antidepressants for acute treatment have an SMD of around 0.30.[4,5,19] On average, psychotropic drugs are no less effective than many medical treatments considered standard of care.[19] What is actually overestimated is what we expect a drug to accomplish on its own, in psychiatry as well as in any other medical specialty.

There is, of course, a compelling counterargument. The evidence is fraught with publication bias and poor methodological design, and nonspecific trial factors –clinical setting, expectations, and the quality of the relationship with the investigator– can strongly affect outcomes, often to a degree comparable to the active drug.[5,9,10] Hengartner and Plöderl estimate that the minimal important difference (MID) on the HAM-D-17 should be between 3 and 5 points, above the average difference observed.[8] We must take this very seriously. However, there is a considerable conceptual, rather than numerical, leap from acknowledging these shortcomings to embracing the nihilistic conclusion that antidepressants "do not work."[21] More nuanced evidence, such as that presented by Vöhringer and Ghaemi, points to a conclusion that is uncomfortable for both extremes: antidepressants are clearly superior to placebo in moderate and severe depression and probably ineffective in mild depression.[11] They are one therapeutic tool among others, with specific indications.

However, the discussion extends beyond methodological considerations. Its limitations become apparent when population averages are transferred directly to clinical practice, where they encounter individual life histories. In the everyday reality of outpatient practice, emergency departments, and inpatient units, we treat patients with widely differing clinical presentations, histories, and comorbidities. Our clinical impression is that the "effect size" of an appropriately prescribed antidepressant, accompanied by adequate clinical care, is often much greater than the average of 0.3. Why? Because clinical practice is not a randomized controlled trial (RCT).

Three reasons explain this difference between the average effect observed in trials and what we see in real-world clinical practice. First, medication does not act in a vacuum. A pill is part of a treatment plan that may include psychotherapy, lifestyle changes, and sustained clinical support; therefore, what we measure as the "drug effect" in real life is a complex combination of pharmacology, placebo effects, the therapeutic relationship, and hope. Second, we do not treat the "average patient." Most RCTs exclude patients with comorbidities, personality disorders, suicide risk, or substance use. In contrast, in clinical practice we work with precisely this complexity, including the acute risks that trials often exclude for ethical and methodological reasons. Third, suffering is not linear. A 3-point reduction on the HAM-D may be trivial for someone experiencing mild distress. Still, for a person at the height of panic or hopelessness, it may be the step that allows them to breathe again –a qualitative shift from despair to being able to sustain everyday life that no SMD can capture.

No number can fully capture what it means for someone who thought about dying every day to begin, quite simply, to feel that getting up in the morning is worthwhile. In everyday clinical practice, medication`s effect rarely occurs in isolation. It emerges within a therapeutic setting shaped by the trust or mistrust that the patient brings to the clinical encounter. A clinician who takes the time to explain what to expect from the medication, carefully considers how information is conveyed, and builds a strong therapeutic alliance is working with more than a molecule. The clinician is engaging a distinct phenomenon, separate from the drug itself, that the literature calls the placebo effect.[22]

The evidence supports this view. The *NIMH Treatment of Depression Collaborative Research Program* showed that the therapeutic alliance significantly predicts clinical outcomes with active pharmacotherapy, placebo, and psychotherapy, operating as a relevant factor across all treatment modalities.[23]

A recent observation by Burke in *The Lancet Psychiatry* notes that, in contemporary trials of therapeutic devices for depression, remission rates in placebo groups have reached 41%.[22] Burke proposes understanding this phenomenon as an active mechanism that can be ethically harnessed in clinical practice through the quality of the therapeutic setting and the therapeutic relationship.

In this article, we understand the placebo effect as the organism's capacity to mobilize psychobiological mechanisms of healing through belief and the therapeutic relationship.[22] It exists independently of the drug and operates in any therapeutic intervention when conditions allow. The clinically relevant question today is how to harness it for the patient's benefit, particularly in severe conditions, where every therapeutic resource matters. In practice, the drug's effects and an effectively elicited placebo response can reinforce one another, and this synergy can produce outcomes that medication alone would be unlikely to achieve.

All of this plays out in the consulting room. When we sit across from a suffering patient, what we do in the first few minutes matters. The way we look at the patient, the time we devote to them, the information we provide about the medication, what we promise and

what we do not, and the quality of the listening they receive are dimensions that a trial does not capture but that are reflected in outcomes. They are fundamental to treatment. Some psychiatrists recognize this from the very first consultation, while others take longer to appreciate it. You cannot see the difference between them on a Hamilton scale or in a meta-analysis, but you can see it in the consulting room. It shows up in who improves and who does not, who continues treatment and who drops out, which patients begin to reclaim their lives, and which remain suspended in partial improvement. This is the clinical dimension that trials fail to capture and that professional practice needs to recognize.

What a healthcare system considers a "sufficient" therapeutic effect is not merely a technical question. It also entails a decision about the level of suffering that society is willing to tolerate before intervening. This may be described as a *politics of suffering*: the set of implicit decisions, often invisible even to those who make them, through which avoidable suffering is distributed across individuals and thresholds are established for determining whether that suffering warrants a clinical response. Canguilhem showed that defining what is normal and what is pathological always involves a value judgment.[24] Adopting an excessively restrictive standard of clinical relevance amounts, under the guise of methodological rigor, to tacitly accepting that the subthreshold suffering experienced by many people does not merit intervention. Medicalizing every form of distress produces the opposite effect and leads to the trap denounced by Illich: the expropriation of people's capacity to cope with their own vulnerability.[25] Between these two extremes lies an ongoing clinical and conceptual task that every professional undertakes, consciously or not, each time they decide to prescribe medication, postpone its use, or forgo it altogether.

There is a more responsible path than either statistical purism or indiscriminate medicalization. It requires maintaining a healthy skepticism toward both enthusiasm and nihilism, selecting more carefully whom we treat with medication, reserving antidepressants for moderate to severe depression and anxiety accompanied by clear functional impairment, and explaining honestly what that "small effect" actually means.

In clinical practice, that explanation might sound something like this: studies show that, on average, the medication provides a modest improvement. It is far from a cure, but for many people, that difference, although quantitatively small, may be enough to enable them to continue psychotherapy, return to work, or make everyday life feel less unbearably burdensome. Medication should therefore be presented realistically, as one tool among others within a broader therapeutic process, with the decision of whether it is worth trying in a particular situation made jointly with the patient.

It is also important to bear in mind that antidepressants do not act solely by relieving symptoms. Growing evidence indicates that they induce neuroplastic changes through direct biological mechanisms, including increased BDNF (brain-derived neurotrophic factor), hippocampal neurogenesis, and modulation of synaptic plasticity through direct binding to the TrkB (tropomyosin receptor kinase B) receptor.[26,27] These mechanisms are distinct from the placebo effect. However, their effects may be enhanced in the clinical encounter when the therapeutic alliance, setting, and quality of care activate additional psychobiological processes. Although not a cure in itself, this neuroplastic substrate opens a window of brain plasticity that placebo alone does not produce. What occurs within that window –the psychological work the individual can sustain within a high-quality therapeutic relationship– determines whether these changes translate into lasting recovery or whether symptoms return after the medication is discontinued.

Finally, what is commonly called the "placebo" should be recognized as an expression of the power of ritual, expectation, and, above all, the therapeutic relationship. Far from opposing pharmacology, careful attention to the therapeutic setting is part of the treatment's effectiveness. Choosing the appropriate drug matters, but so does how it is prescribed, the context in which it is prescribed, and the meaning jointly attributed to it.[5]

Ultimately, this means holding two statements that coexist without contradiction: antidepressants have, on average, a modest effect, and a meaningful proportion of that effect depends on placebo effects and context. For a particular person at a particular moment, that additional benefit may make the difference between continuing to sink and beginning to recover.

Between the paper and the person lies a space in which what matters most is at stake. Clinical judgment occupies that space, grounded in honest conversation and an ethics of care. Behind every SMD is an individual life story struggling, as best it can, to reclaim some form of life of its own.

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