

Closing the treatment gap: expanded access as the next step in psychiatry

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Introduction

A psychiatrist receives the following message from the family of a patient after her death:

"A lot of people were surprised by her steep and rapid decline. My goal had always been to keep A home as long as I could. I am happy that I did keep her home, and the kids and I were with her when she passed at age 75! I want to thank you for all you did to access and help A in the clinical study. I believe that drug and study added a few years to her life so we could enjoy one another. I will miss her like crazy".

This message captures what is often overlooked in discussions about clinical trials and drug development: investigational treatments are not only scientific opportunities, but also opportunities for patients and families to gain meaningful time, preserve independence, and maintain quality of life when standard treatments have failed.

For many individuals with severe mental illness (SMI), however, access to emerging therapies remains limited. Approximately 14.2 million people in the United States live with SMI, including schizophrenia, bipolar disorder, severe depression, and neurodegenerative diseases. Treatment resistance affects an estimated 20–60% of these patients, leaving many with persistent symptoms, repeated hospitalizations, dependence on long-term care, and substantial functional impairment [1].

A systematic review evaluating mortality in SMI analyzed 76 studies and found significantly higher all-cause mortality among individuals with schizophrenia (RR 2.89, 95% CI 2.50–3.34) and bipolar disorder (RR 2.51, 95% CI 2.10–3.00) [2]. In addition, the physical health burden associated with SMI emerges early. A 2024 systematic review found that individuals with SMI have more than twice the odds of developing physical multimorbidity compared with those without SMI (OR 2.4) [3].

Despite this significant burden, psychiatry continues to face substantial unmet medical needs in treatment—resistant mood disorders, schizophrenia, neurodegenerative diseases, suicide prevention, and substance use disorders. At the same time, innovation in psychiatric drug development has remained limited, with most medications introduced over the past 13 years representing incremental advances rather than transformative breakthroughs. Compared with other medical specialties, psychiatric drug development continues to lag in novelty, therapeutic impact and the ability to address some of the field's most urgent clinical challenges.

These realities raise an important question: when patients with SMI have exhausted approved treatments but remain significantly impaired, should psychiatry do more to provide access to promising investigational therapies?

Expanded Access (EA)

EA programs, also known as compassionate use or preapproval access, allow eligible patients with serious or life-threatening conditions to receive investigational therapies. These programs are intended

for patients who have exhausted approved treatment options and are unable to participate in ongoing clinical trials. The investigational therapy must show sufficient promise, and the treating physician must determine that the risks of the therapy are not greater than the risks posed by the underlying disease [4]. Because these treatments have not yet completed the full approval process, their safety and effectiveness remain uncertain [1].

Nevertheless, EA provides an important opportunity for carefully selected patients with refractory illness to consider potentially beneficial therapies. It may also help address the limitations of traditional clinical trials, as strict eligibility criteria can prevent some patients with complex and severe illnesses from participating, leading to the underrepresentation of certain real-world clinical populations in research settings.

Why Psychiatry Has Fallen Behind: Barriers to EA

Despite significant unmet needs in psychiatry, EA remains rarely used. A systematic review conducted in the Netherlands identified only 14 EA programs in psychiatry, with just 4 active in 2023, despite approximately 7,000 psychiatric clinical trials having been conducted [1].

Several factors may contribute to this disparity. Vermeulen and colleagues [1] suggest that psychiatry has comparatively less research involving EA and that the availability of multiple treatment approaches—including psychotherapy, social interventions, rehabilitation, and pharmacologic treatments—can make it more difficult to define when all reasonable options have been exhausted [1]. Additionally, psychiatric illness is often framed differently from other serious medical conditions. While oncology EA is commonly considered in the context of limited survival, psychiatric urgency may involve treatment-resistant disability, suicide risk, malnutrition or catatonia, which may not align with regulatory frameworks that emphasize mortality-based outcomes.

Other barriers include limited sponsor incentives and reimbursement challenges. Sponsors may decline EA because drug supplies are limited, resources are needed for clinical trials, and EA must not compromise studies supporting regulatory approval. Safety reporting requirements, logistical challenges, and administrative burden may further limit participation. Psychiatrists may also be more reluctant to pursue investigational therapies as a last resort [1]. Clozapine illustrates this broader challenge. Despite being the most effective treatment for treatment-resistant schizophrenia, it remains substantially underutilized. If even an established FDA-approved medication with demonstrated efficacy is often introduced late in the course of illness, it is not surprising that EA programs remain uncommon.

Balancing Access, Safety, and Scientific Responsibility

EA requires balancing access to promising therapies with appropriate safeguards for safety and effectiveness. It should complement, not replace, clinical trials.

Even when appropriate, obtaining investigational therapies requires physician assessment, manufacturer agreement, IRB approval, and FDA submission. Additional barriers include medication costs when manufacturers do not provide treatment free of charge. Although FDA approval is rarely the main obstacle, practical barriers before and after submission often limit access.

Post-trial access represents another challenge. Only 29.5% of clinical protocols mention post-trial access in any form, and one review found that none provided actual continued access after trial completion [5]. Legal requirements for post-trial drug provision exist in only five countries: Argentina, Brazil, Chile, Finland, and Peru, while the United States and Europe have no legal obligation [6]. This creates an important gap for patients who benefit from an investigational therapy but lose access when the sponsor discontinues the trial.

Lessons From Oncology: Group C and the Evolution of EA

Oncology provides an important example of how coordinated EA pathways can develop. The group C program, created through collaboration between the National Cancer Institute, the FDA, and cancer cooperative groups, allowed physicians to prescribe selected investigational cancer medications outside traditional clinical trials through NCI-affiliated pharmacies.

The program maintained safety monitoring while allowing evidence to accumulate through clinical experience. Group C became an early population-level EA model and demonstrated that access to promising therapies could coexist with scientific oversight, helping shape modern FDA flexibility. Its success raises an important question for psychiatry: whether similarly coordinated approaches could be developed for patients with severe, treatment-resistant disorders who have exhausted available treatments.

Creating a More Effective EA System in Psychiatry

If EA is to become a realistic option in psychiatry, the current barriers must be addressed. Several recommendations have been proposed to improve the EA, including that pharmaceutical companies prospectively determine whether they intend to establish EA programs for investigational drugs. Other recommendations include creating a centralized registry of EA programs, establishing independent review committees to determine patient eligibility, developing coordinating centers to streamline applications, securing financial support for treatment costs, improving regulatory pathways, ensuring that patients understand the limited evidence supporting investigational therapies, and developing secure technical platforms to facilitate EA requests [4].

Many of these recommendations address practical barriers that currently limit access for patients and clinicians. The absence of a centralized system remains one of the greatest obstacles, leaving physicians and patients responsible for navigating a complex process with limited information about available opportunities.

Conclusion

EA will not replace clinical trials or eliminate the uncertainty inherent to investigational treatments. However, it provides an important pathway to carefully selected patients whose illness remain refractory despite available therapies and who have no other meaningful options.

Psychiatry has an opportunity to develop more effective approaches for responsibly connecting patients with promising innovations while maintaining appropriate safeguards. For individuals and families facing severe illness, access to an investigational therapy may represent more than a treatment opportunity; it may represent additional time, function, and quality of life.

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