PAREA
PSYCHEDELIC ACCESS AND RESEARCH EUROPEAN ALLIANCE

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PAREA Position Statement

Leveraging the EU Pharmaceutical Package

A Life Cycle Approach to Address High Unmet Needs and Foster Mental Health Innovation by Incentivizing Psychedelic Novel Medicines

INTRODUCTION

Unmasking the blind spot in European pharmaceutical legislation

European medicines reform must prioritize meaningful, needs-driven innovation that places patient and public health at the forefront. With one million Europeans lost to suicide since 2016, we must ask: Are we overlooking a critical blind spot by not sufficiently incentivizing R&I in innovative mental health treatments, an area of profound unmet needs and societal impact?

Half of the population will experience mental illness during their lifetime, according to the OECD[1]. The World Economic Forum's Global Risks Report 2023 identifies mental health deterioration as a significant risk to economies and societies[2]. 7.2% of people in the EU, i.e., 32 million, suffer from chronic depression[3], a disorder which carries significant risk of suicide. WHO Europe estimates that 3 out of 4 people suffering from major depression do not receive adequate treatment[4]. Incomplete treatment response or treatment resistance has been described in up to 50 % of the treated patient population[5]. Tragically, almost one in three people with treatment-resistant depression will attempt suicide at least once in their lifetime[6]. 130 000 people die by suicide every year in Europe[7], meaning that between 2016 and now, one million Europeans lost their lives to suicide. People with severe mental disorders die 10 to 20 years earlier than the general population[8]. Depression increases the risk of anxiety disorders, substance abuse disorders and other non-communicable diseases, such as diabetes and heart disease. The opposite is also true, meaning that people with these other conditions have a higher risk of depression.

Our response to the rising tide of mental health disorders is alarmingly inadequate. A recent EC discussion paper titled "Scoping study on evidence to tackle high-burden under-researched medical conditions" found that mental disorders top the list[9]. The number of EU-approved therapies for mental health conditions are shockingly low. For instance, last year, none of the 89 new medicines recommended for approval by the EMA were for mental health conditions . Globally, only seven neuropsychiatric drugs have been approved since 2015, while the field of oncology has seen approvals of 80 drugs[11]. How innovative are these new psychiatric drugs? The former director of the US National Institute for Mental Health, Thomas Insel offers an answer: "Today there are about 30 different antidepressants, 20 different antipsychotic drugs, seven different mood stabilizers used in bipolar disorder, and [six] different classes of drugs for ADHD. Almost none of these are more effective than the medications we had [three] decades ago, although newer medications have different and, in some cases, better side-effect profiles." [12]

These stark disparities illustrate a disconnect between existing incentives and commercial R&D choices on the one hand, and the most vital human needs for left unaddressed on the other.

Thankfully, innovations that can significantly improve patients' lives continue to emerge, and psychedelic compounds are one such extremely promising area. There are 16 ongoing clinical trials with psychedelic compounds in the EU for a range of brain health conditions as well as for alleviating existential distress in end-of-life care.[13] **Unlike other antidepressant medications, psychedelic therapies address the root cause of the disease and can provide long-lasting benefit to many severe mood disorders with just one or a few administrations.** Eventually, they could curb chronic use of anti-depressants and mitigate chronic healthcare system resource use through the enduring benefit of therapy sessions[14].

INNOVATION & INCENTIVES

Meeting high unmet needs in mental health with psychedelic therapies

The European Charter of Patients' Rights enshrines the right to innovation, and the 2022 Versailles Declaration underscores the EU's ambition to become a leader in biomedicines. This should serve as a clarion call for the mental health sector, where there is a pressing need to incentivize the development of novel mental health treatments, such as psychedelic therapies.

PAREA calls for the review of EU pharmaceutical legislation to be leveraged as a critical tool to foster innovation and support the development and deployment of innovative mental health treatments. Psychedelic therapies, with their potential to revolutionize mental health care, should be at the forefront of this effort. This approach can position the EU as a global leader in this field and enhance the EU's biomedical capabilities.

Access to medicines is conditional on the development of suitable treatments and is substantially shaped by how the market incentivizes and rewards innovation. The EU has demonstrated a successful approach to incentivizing R&D in the realm of orphan medicines. Since 2000, over 200 orphan medicines have been authorized for the benefit of patients suffering from rare diseases[15]. Likewise, the EU's successful incentivization of paediatric medicines offers a valuable model - the Paediatric Regulation has spurred increased R&D, leading to many new treatments. The current discussions on incentivizing the development of antimicrobials are another positive example.

In this context, PAREA supports a recent position paper by Austria, Belgium, Ireland, Luxembourg, and the Netherlands titled "Applying a Needs-Driven Approach to Pharmaceutical Innovation[16]." The paper proposes the development of a "graded classification" of unmet needs based on standardized criteria. This could guide governments in deciding which research to fund and which drugs to reimburse, enabling a lifecycle approach, more strategic use of public research funding, the creation of needs-driven incentives, and prioritization of reimbursement for suitable innovative treatments.

PAREA calls for a clear definition of unmet needs associated with the most significant societal health benefits. This definition must recognize and prioritize mental health conditions, which carry a heavy burden of mortality and morbidity and have seen stagnated innovation for several decades. Based on the clinical research thus far, novel psychedelic treatments show promise of exceptional therapeutic advancement in reducing mortality and morbidity in several mental health conditions and substance use disorders. As such, these treatments should be adequately prioritized and incentivized.

However, these therapies face unique challenges, including stigma, their legal status, lack of extensive and long-term evidence, standardization issues, and lack of public funding, particularly for non-profit researchers. Furthermore, a lack of anticipatory attention towards access risks creating a bottleneck effect where psychedelic medicines are only available to the wealthy, leaving those most in need without access. This includes lower-income, socio-economically deprived communities, which are disproportionately affected by mental health problems and addictions.

PAREA calls for a concerted effort to address these barriers. This must involve the EU and member states support in developing an infrastructure for safe, equitable, and affordable access to psychedelic medicines, building capacities that mirror those in other healthcare professions, and educating medical professionals, HTA bodies, payers, and citizens to recognize psychedelics as medicines. By building a necessary infrastructure and fostering a conducive and predictable environment for reimbursement decisions, we can ensure that the benefits of psychedelic therapies are accessible to all, thereby avoiding the perpetuation of existing inequalities.

Stigma, complexities surrounding the patenting and commercialization of psychedelic treatments, and the non-involvement of established pharmaceutical companies have all hindered progress. These therapies, which can lead patients into remission after a limited number of sessions, challenge the prevailing prescription-based business model. As a representative from Goldman Sachs famously pondered, *"Is curing patients a sustainable business model?"* [17]

PAREA calls for the creation of new business models to address the shift in cost from chronic to one or several treatment sessions. Moreover, large pharmaceutical companies should be incentivized to conduct more extensive trials to generate more data. In doing so, commercial incentives need to be balanced with public health needs, and the traditional knowledge of Indigenous communities informing clinical developments with psychedelics needs to be acknowledged and rewarded.

Currently, the majority of R&D efforts in the field of psychedelic therapies are undertaken by start-ups and smaller biotech companies. These entities face considerable challenges in securing funding to conduct large clinical trials, further compounded by complex regulatory requirements.

PAREA calls for an infusion of public funds to make psychedelic research more equitable and inclusive, and for a comprehensive package of incentives for smaller developers. Such incentives could include support via public funding and grants, complimentary scientific advice, fee reductions, and fostering interactions between medicine developers, regulators and HTA bodies focused on generating optimal and robust evidence that satisfies the needs of both regulators and national HTA bodies.

PAREA aligns strongly with the European Parliament's 2021 “Access to medicinal products” resolution, which “calls on the Commission and Member States to promote independent research in areas of public health interest insufficiently addressed by commercial research”. The resolution emphasizes the need for public funds to support R&D where the industry has been reluctant to engage, and advocates for a stronger link between public investment in research and unmet needs. It also endorses the social responsibility of the pharmaceutical sector.[18]

PAREA calls on the EU regulators to explore how academia and non-profit organizations can best contribute to the development of psychedelic innovative medicines, and how EU policies can favour an academic-driven pathway for their development.

A CALL FOR COMPREHENSIVE OVERSIGHT:

Navigating the complexities of combination therapies.

The current regulatory system, designed for traditional medicines, falls short in addressing the complexities of combination therapies, such as psychedelic therapies, which inherently blend pharmacological intervention with therapeutic support. These therapies cannot be taken at home and require administration by qualified medical staff.

Given that regulatory bodies focus on assessing the safety and efficacy of medications, this leaves the psychological support component under-researched. This lack of a comprehensive regulatory framework could lead to the implementation of untested and potentially harmful practices, particularly for vulnerable patients. Psychedelic novel therapies necessitate the establishment of standardized guidelines for the clinical practice of therapy or psychological support in conjunction with psychedelic medications. Moreover, the broader medical ecosystem must incentivize therapists to integrate these new treatments into their clinical practice.

PAREA calls for recognizing innovative care pathways that combine pharmacological, psychological, and digital solutions. The EU should support the generation of empirical evidence for the quality and safety of psychological support provided alongside psychedelic medicines. This includes understanding the interactions between the drug effects and the psychotherapy as well as assistive technologies that can support patient preparation, monitoring, treatment integration, and more.

The regulation of combination products, particularly those involving digital or psychedelic therapies, is complex. It includes determining how to manage post-market surveillance, or how to disentangle the interaction between the different components of the treatment. A new, dedicated body could provide more specialized expertise in these areas.

PAREA calls for the EMA to set up a new committee or centre of excellence on combination products to facilitate the development and approval of these therapies. This would streamline the regulatory process, provide more clarity to developers, and ensure that such products are properly evaluated for safety and efficacy. Psychedelic therapies should be included in its scope.

EMBRACING THE FUTURE

Embracing real-world evidence, digital technologies, and innovative trial designs

The approval of psychedelic novel therapies necessitates a comprehensive understanding of their safety and efficacy. Rigorous application of real-world evidence and digital health technologies can supplement traditional confirmatory trials.

PAREA calls for the employment of the RWE and digital therapeutics to enhance pre- and post-authorisation assessments, support identifying optimal and personalized treatment protocols, and thereby facilitating the development of therapies that are safe, effective, cost-efficient and individualized.

Psychedelic therapies have shown promise in treating a broad spectrum of mental health conditions, many of which share the common feature of being internalizing disorders. These include depression, addictions, OCD, and anorexia, where patients often engage in persistent negative thinking or rumination. Psychedelics show a promise in disrupting the activity in systems and circuits that encode these thought and behaviour patterns, allowing for a recalibration as the acute effects of the drugs subside.

PAREA calls for supporting innovative trial designs to explore the trans-diagnostic properties of psychedelics. One such design is the basket trial, which tests the effect of a single drug on a single biomarker across multiple disease states.

PAREA calls on the EU to subsidize multi-arm, multi-stage platform trials and umbrella trials with psychedelic compounds. These trial designs allow for the simultaneous testing of multiple treatments or therapeutic questions within a single protocol and control group, potentially accelerating the development process and increasing the likelihood of identifying effective treatments.

The pharmaceutical legislation should encourage these innovative research methods while upholding high standards of safety and scientific rigour. It should also foster collaboration among healthcare payers, industry, and end-users to fund and participate in these research initiatives. This approach will not only expedite the development and implementation of psychedelic novel therapies but also boost our understanding of their safety and efficacy.

SPECIAL ACCESS

Compassionate use programmes and conditional marketing authorisation

This year, Australia became the first country to officially regulate the medical use of psychedelics for the treatment of PTSD and treatment-resistant depression[19]. It is expected that the first psychedelic therapies will be approved in the US in 2024. Also in 2024, the UK drug regulator, MHRA, will introduce reciprocal drug approvals with the US to accelerate access to new treatments. Consequently, UK approvals of psychedelic therapies might occur soon after the US ones. Because psychedelic drug developers prioritize the US market and clinical trials in Europe are not sufficiently advanced, approvals in the EU might happen several years after those in other countries. This delay could put EU patients at a significant disadvantage and pressure on access to these treatments might lead some people to explore access outside the medical model, exposing them to potential risks of unregulated and unsupervised practices.

Given the huge unmet needs in the area of mental health, **PAREA calls for** the EU to provide early access to novel psychedelic treatments to patients who need them most through means like compassionate use programmes and conditional marketing authorisation, following approvals by regulators like the US FDA. In addition to facilitating patient access, these programs can play a crucial role in providing real-world treatment experience for providers and generating valuable real-world data to inform safety policies and future product labelling.

PAREA calls for the use of early access pilot programs to treat a diverse set of patients with complex comorbidities who are often excluded from clinical trials with psychedelic compounds. By allowing these patients access to psychedelic medicines, we can gather critical additional data on the safety and efficacy of these treatments in a broader population. Furthermore, these programs can explore different treatment protocols, such as group therapy and peer support specialists, to find the optimal balance of safety, efficacy, affordability, and equitable access.

Compassionate use of these therapies is particularly relevant in the context of palliative care. It is estimated that between 24% to 70% of palliative care patients suffer from depression[20], and the Commission has committed to reducing human suffering and focusing on the specific needs of vulnerable groups.

PAREA calls for the urgent consideration of compassionate use of psychedelic medicines. These could provide an alternative pathway for alleviating end-of-life suffering and treating existential anguish in people with life-threatening illnesses, as is already happening in Canada with psilocybin.

OFF-LABEL COMPLEXITY

Navigating the complexities of off-label use in psychedelic therapies

The EU pharmaceutical revision underscores the importance of ensuring that medicinal products are safe, of high quality, and effective for use in the target population, a principle that should extend to off-label use, necessitating rigorous scientific evidence and ethical guidelines.

Off-label use, when supported by evidence, can increase access to safe and potentially transformative treatments. All the while, the unique nature of psychedelic therapies necessitates comprehensive guidance on future off-label use. The selection of suitable patients for such treatments requires a careful risk-benefit analysis, considering the severity and duration of the patient's condition, previous treatment history, and the urgency for treatment.

The competence of healthcare professionals administering these treatments is paramount. Without relevant training, physicians may not be able to competently treat patients with serious conditions. Therefore, while off-label use may provide access to promising treatments, it must be done responsibly, with robust training criteria, standards of care, and regulatory oversight.

PAREA calls for adequate regulatory oversight to ensure patients' safety in the area of future off-label use of psychedelic therapies. Comprehensive guidelines should be developed, taking into account ethical and legal dimensions.

CONCLUSIONS

Advocating for a new social contract regarding mental health innovation and care

Regulatory systems are increasingly out of sync with contemporary science and technology. PAREA welcomes the much-needed EU pharmaceutical package reform and outlines solutions aimed at addressing the massive unmet needs in mental health by incentivizing breakthrough innovation across the full lifecycle of psychedelic therapies. We underscore the need for a comprehensive, collaborative, and future-proof approach to mental health novel care, treatment, and research funding. The goal is to foster a dynamic and competitive R&D environment in the EU for novel mental health treatments, such as psychedelic therapies, and ensure that these potentially transformative therapies are accessible, safe, and affordable to those who need them most.

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Who Are PAREA?

We are a non-profit, membership-led, multistakeholder and multidisciplinary partnership. We bring together patient organizations, medical associations, scientific societies, umbrella coalitions, psychedelic foundations, and for-profit sector.

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OUR MEMBERS

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