Journal of Mental Health & Well-being (JMHWB)

VOLUME 1 ISSUE 1 (2025)

PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

Journal of Mental Health & Well-being (JMHWB)

Volume 1 Issue 1, Year 2025
https://journals.e-palli.com/home/index.php/jmhwb

A Biotechnological Outlook on Stem Cell Therapy for Neuropsychiatric Disorders

Aman Tiple[1*], Shiwani Kawade[2]

Article Information

Received: April 25, 2025

Accepted: May 31, 2025

Published: June 30, 2025

Keywords

Biotechnology, Brain Organoids, Cell Therapy, Disease Modeling, iPSCs, Neural Regeneration, Neuropsychiatric Disorders, Stem Cells

ABSTRACT

Neuropsychiatric disease is a major global health burden, and an important part of its challenge is the complexity of its etiologies and the modest response to many therapy options. Conventional treatments typically palliate rather than address the underlying disease process, often resulting in residual disability for many patients. Stem cell therapeutic approach, on the basis of the distinctive characteristics of undifferentiated cells, is an attractive biotechnological horizon for treatment of these diseases. The aim of this review is to describe the current state of the field, covering the basics of stem cell biology, the various applications for modeling/neuropsychiatric disease understanding, and neural repair. It also explores the significant technical, ethical, and economic challenges that need to be addressed. Lastly, it reviews up-to-date advances in preclinical and clinical applications, future perspectives and translational routes, such as combination with the latest technologies and regulatory aspects, to bring these potential therapies closer to clinical reality.

INTRODUCTION

Neuropsychiatric diseases include many diseases that affect the nervous system and brain and adversely affect cognitive functions, emotions, behaviors and social functioning. Prominent among these are depression, schizophrenia, bipolar disorder, anxiety disorders and neurodevelopmental disorders such as autism spectrum disorders. These diseases represent an enormous burden for individuals, families, and healthcare systems globally. The pathophysiology is usually multi-factorial, including some genetic, environmental and complex dysregulatory changes in neural networks. Although the disease has been the subject of decades of investigation, the precise mechanisms that underlie these diseases remain only partially elucidated, making the targeted and curative development of disease-modifying therapies very challenging.

Existing treatments of neuropsychiatric disorders are mainly based on pharmacological, psychological, or neuromodulatory interventions. Although they offer relief to many patients, they also frequently present limitations. Pharmacotherapy (e.g., antidepressants, antipsychotics) can be associated with significant side effects, individual differences of efficacy and may not target all symptom domains. Furthermore, they generally just treat symptoms- not actually fix or heal damaged neural tissue or normalise underlying circuit dysfunction. Psychotherapy assumes patient interest and access, both of which may be obstacles. Neuromodulation methods such as deep brain stimulation and transcranial magnetic stimulation, are typically applied in extreme cases that do not respond to other treatments, and are generally invasive or semi-invasive. Given that several neuropsychiatric diseases are chronic disorders and evidences of continuous neurobiological deterioration in some, it remains challenging that disease-modifying therapeutic interventions to recover from pathological brain to healthy brain is set to be explored.

Shortcomings of available treatments indicate the urgency of new therapeutic strategies that can treat the underlying causes of these diseases. Targeted therapies and biotechnology have evolved into common paradigms for therapeutic application, with stem cell technology, in particular, an attractive new frontier. Stem cells, with their capacity for self-renewal and potential to differentiate into many cell types, offer promise to model disease processes, to discover new drug targets and, most grandly, to replace damaged or dysfunctional neurons and neural circuits. The potential to engraft with native neural circuitry and release neurotrophic factors is advantageous for the intricate molecular and cellular deficiencies that underlie neuropsychiatric conditions. This review article examines the Stem Cell biotechnology application as a transformative perspective, reviewing the elemental science, current research, challenges associated with it and the future directions for the cure of Neuropsychiatric conditions.

LITERATURE REVIEW

Neuropsychiatric Disorders and Current Treatment Landscape: Overview and Limitations

Neuropsychiatric diseases are a heterogeneous group of diseases that affect the central nervous system and are identified by changes in mood, cognition, behavior, and mental functions. For example, major depression specifies sustained low mood, anhedonia, and alterations in sleep, appetite, and energy. Its pathogenesis is believed

[1] Vasishth Genomics Research Lab Pvt. Ltd., Bangalore, India
[2] Institute of Biosciences and Technology, MGM University, Chh. Sambhajinagar, 431001, India
[*] Corresponding author's e-mail: amantiple97@gmail.com

to result from multiple gene-environment interactions, environmental stress, and impairment of neurotransmitter systems, and neural circuitry, especially in regions such as prefrontal cortex and hippocampus.

Schizophrenia is a serious and lifelong struggle with how a person thinks, feels and behaves. Manifestations of the illness typically are hallucinations, delusions, disorganized thinking, and negative symptoms such as avolition and flattened affect. Neurobiological investigations implicate structural and functional anomalies in several brain areas, derangements in dopamine and glutamate pathways, and putative neurodevelopmental disturbances. Bipolar disorder is characterised by episodes of mania or hypomania and depression. Neurobiological bases are multifaceted and involve disruption of circuits and neurotransmitter systems related to emotional processing. Anxiety and obsessive-compulsive disorders, post-traumatic stress disorder and neurodevelopmental disorders like autism spectrum disorder and attention-deficit/hyperactivity disorder are other common neuropsychiatric disorders. Although they have different diagnostic criteria and symptomatic domains, many of them share neurobiological similarities such as synaptic dysfunction, neuronal loss or disrupted connectivity inflammation, and dysfunctional neurogenesis of certain regions in the brain. Identification of these common and distinct pathogenic processes is paramount for the development of potential therapies.

Although there has been considerable advancement in the field of psychopharmacology and behavioural therapy in recent decades, present pharmacological treatments for neuropsychiatric conditions are fraught with undesirable side-effects. One of the primary concerns is that not all stain removers are effective. A significant proportion of patients have either incomplete or nil response to initial therapeutic regimens, with chronic illness and dysfunction. For instance, treatment-resistant depression and schizophrenia are still enormous clinical burdens.

The side effects of current drugs are an equally major limitation. Antidepressants can also come with side effects like weight gain, sexual dysfunction or digestive problems. Antipsychotics come with metabolic syndrome, movement disorders (including tardive dyskinesia) and sedation. These adverse effects may compromise patient compliance and quality of life. In addition, these drugs are directed towards symptom control and work by altering neurotransmitter levels, and they do not treat putative underlying neurobiological abnormalities, such as neurotoxicity, glial dysfunction or compromised neural pathways. Generally, they fail to support regeneration or structural restoration of the brain.

Standard diagnostic approaches often fail to capture the full scope of communication deficits in children with ASD. The Early Communication Assessment (ECA) framework categorizes early communicative functioning into nuanced levels and has revealed that preschool children with ASD show severe delays in joint referencing, imitation, turn-taking, and social organization, even when their cognitive abilities appear intact. These deficits correlate more strongly with language delays and symbolic play disturbances than with non-verbal IQ, underscoring the importance of early intervention strategies that go beyond eye contact and physical cues (Singhania, 2025).

Psychotherapeutic treatments, despite being effective for many, are resource-intensive and time-consuming and may not be available to all patients in all settings. Neuromodulation such as ECT, TMS and DBS are effective for severe cases but either invasive, or require access to specific equipment and training and therefore not universally available. The present scenario demonstrates a large void in therapeutic alternatives, especially in patients with more severe or refractory symptoms, and those with diseases in which there is proven neurodegeneration or developmental defect. Clearly, novel therapies that can stimulate neural repair or modulate dysfunctional circuits on a fundamental level, or replace lost cell populations are needed, and stem cell biotechnology is a key participant in that regard.

Stem Cell Biology Fundamentals

Major Types of Stem Cells (Embryonic, Adult, Induced Pluripotent)

Stem cells are a kind of undifferentiated or partially differentiated cell that can proliferate and specialized into many different cell types. This inherent ability attracts a lot of attention from both the regenerative medicine field and the disease modelling field. With respect to therapeutic purposes, there are three major types of stem cells; embryonic stem cells (ESC), adult stem cells and induced pluripotent stem cells (iPSCs). Embryonic stem cells come from the inner cell mass of a blastocyst (a very early-stage embryo). Pluripotent stem cells are defined by their ability to differentiate into all cell types of the three primary germ layers (ectoderm, mesoderm, and endoderm). The capacity to undergo all the steps of development and commitment towards limitless cell types makes ESCs a rich source of potential cells for experimentation and potential therapeutic replenishment. Although significant ethical concerns arise due to their derivation (Patel, 2006; Rousková *et al.,* 2008; Sipp *et al.,* 2018; Volarevic *et al.,* 2018) and their application bears the risk of teratoma formation if undifferentiated cells are remained in the graft (Takahashi, 2009).

Mature stem cells, i.e. adult stem cells, which are found in various places in your body, including your bone marrow, adipose tissue (Barba *et al.,* 2017; Fisher *et al.,* 2016), brain (Shi & Zhang, 2011), and skin (Khodayari *et al.,* 2019). They are multipotent, able to differentiate into few types of cells which is specific to their tissue of origin. For instance, hematopoietic stem cells in the bone marrow can turn into every type of blood cell, and neural stem cells in the brain can become neurons, astrocytes and oligodendrocytes. Compared to ESCs, adult stem cells are more readily accessible and have few ethical problems related to retrieval and have the virtue of minimizing immune rejection by performing an

autologous transplant. True, but they are few in number, and isolating them in culture such that they can be expanded while retaining their function is tricky (Liu *et al.,* 2016; Shi & Zhang, 2011).

Induced pluripotent stem cells (iPSCs) are somatic cells (e.g. skin or blood cells) that have been genetically reprogrammed to an ESC-like state by introducing a defined set of transcription factors. This kind of technology, development by Shinya Yamanaka, launched a new era in the field by providing an alternative source of patient-derived pluripotent cells and removing the ethical concerns related to ESCs (Mazzola & Di Pasquale, 2020; Volarevic *et al.,* 2018). Both ESCs and iPSCs are pluripotent, which means they can differentiate into virtually any cell type, including neural cells that are often affected in neurodegenerative disease models that these cells can be used to either model or in the case of iPSC both model and possibly do autologous cell therapy. Yet, the efficiency and reprogramming safety, potential for genetic abnormalities during the process remains as challenging concern, and the risk of incomplete reprogramming can lead to residual tumorigenic potential (Volarevic *et al.,* 2018).

Mechanisms of Neural Differentiation

The specific differentiation of stem cells into neural cells, such as neurons, astrocytes or oligodendrocytes, is the essential process for significance of these cells in neural and psychiatric fields. The mechanism underlying the differentiation of neurons is a complex process that normally requires duplication of signalling cues and environmental bio-factors to support neural development in vivo.

The differentiation procedures are dependent on the source of stem cells (ESCs, iPSCs, or neural stem cells from adults) and the neuronal type required. In general, pluripotent stem cells (ESCs and iPSCs) are initially directed to a neuroectodermal lineage. This typically involves growing the cells in the presence of growth factors as well as signalling inhibitors that prevent non-neural differentiation trajectories. For instance, blocking BMP signalling and activating WNT signalling are prevalent methods of promoting neural induction.

Subsequent to neural induction, the induced neural progenitor cells (NPCs) are subsequently differentiated into a specific neural or glial subtype. This stage demands tight regulation of multiple growth factors, cytokines and small molecules, in addition to the ability to modify cell culture settings, such as substrate, dimension (2D versus 3D) and composition of growth media. For example, fibroblast growth factor (FGF) and EGF is frequently used to grow NPCs, and its removal or introduction of factors as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3) enhances neuronal differentiation and maturation. These factors have to be present at the right time and at the right concentration for the cell fate to be achieved.

The generation of specialized neuronal subtypes that have been investigated in the context of neuropsychiatric disease, such as dopaminergic (involved in schizophrenia, addiction) and serotonergic (depression, anxiety) neurons or cortical interneurons (schizophrenia, autism), demands more elaborate, kidney-bean shaped protocols that mimic the sophisticated temporal and spatial developmental gradients of cues. Three-dimensional culture systems, such as brain organoids Mazzola & Di Pasquale, 2020; Messina *et al.,* 2020; Pinel *et al.,* 2019), offer a more complex model of tissue architecture that better approximates that of the in vivo tissue and for more extensive neural differentiation and maturation, including ability to form synapses (Tateya & Ito, 2003). It is essential to understand and manipulate these differentiation mechanisms for modelling disease pathogenesis in a dish, and for generating cells for transplantation therapies.

Stem Cell Applications in Neuropsychiatric Research and Therapy

Disease Modeling Using Stem Cells (e.g., 2D cultures, Organoids)

The Stem Cell technology led to the revolution of complex brain disorders by the creation of in-vitro models which are able to mimic the brain development and pathology aspects. There is a great need to develop patient-specific iPSCs for these applications. By reprogramming somatic cells extracted from certain individuals with defined neuropsychiatric diagnoses to iPSCs, researchers have the opportunity to differentiate them into any type of neural cells or organoids that contain the same genetic makeup of the patient, which may model the cellular phenotypes related to the disease.

Two-dimensional (2D) cultures of iPSC-derived neurons, astrocytes and oligodendrocytes facilitate the study of cell-autonomous disease mechanisms. For example, neurons, differentiated from iPSCs of patients with schizophrenia or autism, can differ in morphology, electrophysiology and synaptic connectivity compared to healthy control-derived ones. This enables a venue to investigate how genetic mutations or risk factors affect particular cell types in a human-specific context that was previously confined to the study of post-mortem brain tissue or animal research that may not completely mimic human disease features. In addition, 2D co-cultures involving various neural cell types can be useful for investigations of cell-cell interactions (e.g., neuron-glia communication), increasingly appreciated as relevant in neuropsychiatric conditions. Now, how patient-specific glial cells affect neuronal survival or function can be assessed by the researchers.

We have made significant progress in modelling using three-dimensional culture systems, especially brain organoids. These sophisticated entities, mostly matured from pluripotent stem cells (ESCs or iPSCs), auto-organize into structures that mimic developing brain areas and actually embody more than one cell type along with almost functional neural circuits (Mazzola & Di Pasquale, 2020; Messina *et al.,* 2020; Pinel *et al.,* 2019).

For example, Organoids derived from microcephaly or macrocephaly patients show a size and cellular maturation phenotype that matches the clinical presentation. For neuropsychiatric disorders, organoid models allow us to study altered neurodevelopmental trajectories, cortical layer formation and long-range connectivity deficits that are difficult to model in 2D, in a more relevant environment by providing opportunity to observe processes happening during critical developmental windows. They are valuable resources for understanding the mechanisms of diseases and also for identifying new therapeutic targets.

High-Throughput Screening and Personalized Medicine Approaches

The possibility of producing disease-relevant neural cells en masse from patient-specific iPSCs opens up new horizons for both drug screening and personalized medicine for neuropsychiatric disorders. HTS campaigns can be conducted with these cell lines or organoids to interrogate large numbers of small molecules or genetic perturbations. Investigators can then search for compounds that rescue the observed phenotypes of disease, which may include defects in cellular morphology, calcium signalling, gene expression, or synapses.

For instance, iPSC neurons from patients harbouring a particular genetically definable lesion characteristic of schizophrenia could show decreased synaptic density. HTS assay could be used to discover molecules able to promote synapse formation in these cells. This methodology opens up the possibility to identify therapeutic candidates in a human cellular context, possibly more relevant to clinical endurance, than conventional animal models. It also allows drugs to be tested on cells derived from multiple patients, reflecting the genetic diversity common to many complex diseases.

This idea of personalized medicine in neuropsychiatry is especially intriguing with iPSC technology. IPSCs carry the patient's genetic profile, making the generated neural cells a patient-specific disease model. This allows for testing of various potential drugs or combinations of them directly on an individual patient's cells in vitro. For example, for someone who does not respond to the treatment that usually works, this might help determine the best drug to prescribe to the person or inform a physician that a patient may have an adverse effect to a certain medication based on his or her unique cellular response profile. Although in its infancy for complex neuropsychiatric disorders, this method holds promise for achieving more rational personalized treatment regimens in place of trial-and-error prescription.

Additionally, iPSC-based models can be exploited for the study of the mechanisms driving response to treatment variability among patients. For example, comparing cell phenotypes and drug response in iPSC-derived cells between responder and non-responder for a given medication might identify biomarkers or cell characteristics that predict drug response. This can be led to the development of diagnostic tools which can guide individual's biological profile-based treatment selection.

Potential for Neural Regeneration and Repair

In addition to disease modelling and drug screening, restoration of neural circuits in neuropsychiatric disorders is a prominent therapeutic ambition of stem cell technology. Although gross neuronal loss is not the hallmark of all neuropsychiatric disorders (in contrast to neurodegenerative diseases (e.g., Parkinson's, Alzheimer's), there is accumulating evidence for subtle structural changes, synaptic dysfunctions and deficits in neurogenesis, particularly in the hippocampus and prefrontal cortex, and that are relevant for the symptoms. Several potential therapeutic benefit can be offered by stem cell transplantation.

One possibility is through cell replacement. In disease in which brain neuronal populations are lost or are highly degenerated, the implantation of healthy, differentiated neurons obtained from stem cells (ESCs, iPSCs or adult neural stem cells) could theoretically repopulate the damaged brain region. For example, if certain interneuron deficits lead to circuit imbalance in schizophrenia, transplantation of functional interneurons could potentially remedy such a network disorder. Such a strategy has to overcome critical hurdles of cell survival and correct incorporation into the existing circuitry with limited off-target connections.

Another and probably more immediately reliable mechanism is the paracrine activity of transplanted stem cells. However, even if transplanted cells do not ultimately engraft and survive as replacement neurons long-term, they may release a variety of neurotrophic factors, growth factors and immunomodulating molecules. Such secreted factors may act to increase survival and function of endogenous neurons and glial cells, induce changes in synaptic plasticity, stimulate endogenous neurogenesis, or dampen neuroinflammation (Castillo *et al.,* 2020; Gizaw *et al.,* 2019; Meiliana *et al.,* 2016; Than & Newsome, 2014). This trophic support may alleviate symptoms by improving the health and function of compromised neural circuits without the need for extensive cellular integration.

Secondly, transplanted stem cells, especially adult mesenchymal stem cells of some origin, have immunomodulatory effects Neuro-inflammation has not only been shown to play a role increasingly in the aetiology of various neuropsychiatric disorders. On the other hand, stem cell engraftment may help mitigate this inflammatory response, inducing a more conducive milieu to neural function and repair. Because of the complexity of the brain and the specific circuit deficits in neuropsychiatric disease, regenerative strategies will need to carefully consider the cell type, deliver method, and targeted disorder.

Challenges and Ethical Considerations

Technical and Biological Challenges (e.g., Safety, Integration, Delivery)

The translation of stem cell potential to therapeutic interventions for neuropsychiatric diseases is challenged by a range of technical and biological obstacles. It is a safety concern especially from tumour genesis. ESCs and iPSCs have the ability to proliferate indefinitely and to give rise of teratomas when non-differentiated cells are injected (Takahashi, 2009; Volarevic *et al.,* 2018). Complete differentiation of the transplanted cells towards the desired neural lineage and purification of cell populations to eliminate any trace contaminating pluripotent cells are key factors to diminish this risk. The iPSCs' stability and accumulation potential of genetic abnormalities during reprogramming and expansion also needs the extensive observation.

Another major obstacle is how to successfully integrate transplanted cells within complicated host neural networks. In order to achieve effective functional replacement, transplanted cells need to survive in the host, mature, extend neuronal processes, including axons and dendrites, establish proper synaptic connections with host neurons, and be functionally integrated into the neural network. This is a sophisticated process and requires the 'right' signals from the postnatal environment. Inappropriate integration would be expected to result in abnormal circuit function, and could compound ongoing pathology. Functional integration in the intricate human brain has been challenging, however it has been found in animal models.

Targeting and efficient delivery of the stem cells to a particular region of the brain are also challenging technically. The blood-brain barrier (BBB) limits the infiltration of cells and routes to the brain by necessity are invasive, e.g., direct injection of cells into brain parenchyma. Site, number of cells and mode of injection: where you put the cells, how many and how; to ensure the best survival and spread of cells with least damage to the fragile brain tissue requires extensive research. Related to systemic delivery, modalities that will enable the targeting of cells to the brain and dissemination across the blood-brain barrier are another important concern.

Immune rejection of transplanted cells is also a challenge, even with autologous iPSCs as they may be immunogenic as a consequence of differentiation protocols or genetic manipulation. Immunosuppression could be necessary, which has downsides too. Lines and differentiation protocols can be variable and so one may find that results are hard to replicate, which may just reflect the fact that a quality control process was not in place.

Ethical and Societal Debates

The use of stem cells especially human embryonic stem cells (hESCs), has sparked ethical and societal debate upon their isolation (Patel, 2006; Rousková *et al.,* 2008; Sipp *et al.,* 2018; Volarevic *et al.,* 2018). The central ethical issue involved in hESC research is that of the moral standing of the human embryo from which these cells are derived (Volarevic *et al.,* 2018). Critics say it is wrong to destroy an embryo to obtain stem cells. SG: Supporters highlight the possibility to use hESC to treat patients with severe diseases, the potential medically-related benefits and thus the fact that the latter should outweigh the moral preoccupations about the embryo at such an early stage of development. This debate has been influencing the funding policies and the regulations regarding hESC research in different countries.

Induced pluripotent stem cells (iPSCs) emerged as a solution to the production of pluripotent cells without embryos, thus bypassing some of the moral questions posed by hESCs. However, the development of iPSC technology raises novel ethical questions, including those related to informed consent for donation of somatic cells, the possibility of germline generation or human-animal chimeras from iPSCs, and ethical issues related to the use of iPSCs to produce advanced brain organoids that could demonstrate complex neural activity (Mazzola & Di Pasquale, 2020; Patel, 2006; Volarevic *et al.,* 2018).

Apart the source of stem cells, the clinical use of stem cell therapies pose more general ethical issues. These include the need to have sound scientific evidence of safety and efficacy before widespread clinical use; to curb the spread of unproven and, quite possibly, dangerous "stem cell clinics" that prey on vulnerable patients with empty promises (Volarevic *et al.,* 2018); and to grapple with the ethical issues raised by the prospect of conducting clinical trials in highly vulnerable populations, including those with severe neuropsychiatric illness and potentially impaired decision-making capacity (Gómez-Barrena *et al.,* 2011). The transparent communication with the patient regarding experimental nature and its potential risks of these therapies is crucial.

Economic and Accessibility Barriers

Economic and access constraints will most likely remain barriers that would prevent broad adoption of these therapies, even if they are safe and effective for neuropsychiatric diseases. The process of developing and producing cell-based treatments is difficult and expensive. Establishment of clinical-grade iPS lines, differentiation into specific neural cell types, quality control (QC) monitoring to maintain their purity and safety, and managing a larger-scale production, would involve significant investment in infrastructure, manpower, and QC infrastructure. This makes these approaches expensive for the end therapeutic product.

In addition, the delivery of these treatments, under usual circumstances following invasive neurosurgery for direct brain injection, are as expensive and necessitate the use of specialized medical institutions and well-trained personnel. Post-transplant (post-HTx) care and immunosuppression, as well as ongoing surveillance for safety and efficacy, are additional products. These costs may mean that stem cell therapy becomes inaccessible to many patients, widening existing

disparities and highlighting issues around equitable access to revolutionary treatment. Additionally, more extensive results and development is necessary to bring the stem cell therapy from lab to clinics are lengthy and fund-intensive.

Funding preclinical, toxicity testing, and multi-phase clinical trials is a challenge. The process of gaining regulatory approval for a new cell-based therapy is complex and time-consuming, contributing to cost and time to market. Overcoming these economic and access obstacles will demand alternate funding models (including possibly government subsidies) as well as cost saving and efficiency streamlining in the manufacture and delivery of effective stem cell therapies, if and when proven, to patients in an unrestricted, socioeconomic-agnostic manner.

MATERIALS AND METHODS

The research includes a narrative review enacting to shed the light on the role of stem cell biotechnology in psychiatric diseases. Relevant literature search was performed in databases, including PubMed, Scopus, Google Scholar, and ScienceDirect, using keywords "stem cells," "neuropsychiatric disorders," "iPSCs," "brain organoids," and "cell therapy."

The inclusion criteria focused on peer review articles published between 2006 and 2024, with particular emphasis on recent improvements from 2015. Preclinical studies (in vitro and animal models) as well as studies from early phase of clinical trials have been summed for a more comprehensive and recent view. Papers were chosen on the basis of relevance, scientific application, and the extent to which they were likely to contribute to our knowledge of the use of stem cell therapy in neuropsychiatric indications.

The selection process aimed to identify 5 main themes: stem cell biology, disease modeling, applications in therapy, engineering, and translational hurdles. All references were appraised for scientific quality and relevance to the review objectives.

RESULTS AND DISCUSSION

Recent Advances and Emerging Clinical Insights

Key Findings in Pre-clinical Research

Pre-clinical work in animals and explant stem cell systems remains critical in providing deep insights in how stem cells might mediate treatment of neuropsychiatric disorders. There have also been substantial discoveries related to the survival and engraftment of transplanted neural stem cells (NSCs) or their differentiated progeny in the brain, mainly in rodent models of neurological injury or disease.

It has been reported that grafted NSCs may differentiate into mature neurons and glia in host brain receiving synaptic inputs, and contributing to local circuit activity. Transplantation of NSCs has been investigated in animal models of depression, focusing on the transplantation of NSCs into the hippocampus, which is related to mood regulation and shows reduced neurogenesis in depression. These would-be disease-modifying therapies have uncovered that transplanted cells can survive, differentiate into neurons, and possibly mediate behavioral benefits (although how cell replacement vs. paracrine effects remains unclear).

In disease models for neurodevelopmental disorders, for instance, researchers use iPSC-derived neural cells to investigate such early developmental abnormalities. For example, transplanted human iPSC- derived interneurons in rodent models have been shown to improve local circuit deficits somewhat. In pre-clinical studies, much attention is also paid to optimizing donor cell sources, differentiation protocols to yield defined neural populations, transplantation protocols (e.g. stereotactic injection co-ordinates, cell encapsulation methods) and manipulations to increase cell survival and integration (e.g. co-transplantation with supporting cells, pre-conditioning host environment) (Bolte *et al.,* 2019).

Similar to cellular approaches, microbiota-based interventions such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) have been effective in animal models as well as in some human studies. Such interventions may modify systemic inflammation and restore microbial-derived short-chain fatty acids (SCFAs) involved in neurotransmitter synthesis and microglial maturation, thereby promoting neurodevelopmental outcome. Stem cell therapies that target both neuroinflammation and neuronal architecture would benefit from strategy to correct the microbiota altering neuroimmune pathways to make these therapies more effective in autism spectrum disorder and other neuropsychiatric disorders (Manaf *et al.,* 2025).

Outside of cell replacement, preclinical studies are generating more evidence of therapeutic benefit from paracrine effects. Infusion of different stem cells, including mesenchymal stem cells (MSCs), was demonstrated to bring neuroprotection, anti-inflammatory and pro-neurogenic effects in animal models of brain injury & neurological disease (Castillo *et al.,* 2020; Gizaw *et al.,* 2019; Meiliana *et al.,* 2016). Although most work in such fields has centred around neurodegenerative diseases or stroke, the concept of targeting the brain microenvironment by use of secreted factors might also be relevant in neuropsychiatric disorders, in which neuroinflammation or trophic factor insufficiencies are believed to be involved.

Progress in Clinical Trials and Case Studies

For neuropsychiatric disorders, clinical translation of stem cell therapies is still relatively immature, but less so than for neurodegenerative entities, such as Parkinson's disease, where a few early trials have taken place (Takahashi, 2009). But slowly, early phase clinical trials and case studies using stem cells to treat various neuropsychiatric or neuropsychiatric-related conditions are beginning to trickle in.

Adult-derived stem cells, especially mesenchymal stem cells (MSCs), through IV or intrathecal administration are the most common adult stem cells being evaluated

for the treatment of neurological and psychiatric disorders. These are more often than not phase 1 based trials with primary endpoints focusing on safety and tolerability. While there might be anecdotal reports or fairly limited case series that hint at the possibility of benefit, we usually don't have solid evidence of efficacy from well-controlled trials in groups of patients for the core neuropsychiatric symptoms (such as depression, hallucinations or cognitive deficits).

For disorders with relatively clearer neurodegenerative aspects, or conditions in which neuroinflammation might have a higher profile, such as multiple sclerosis (MS) or some rare genetic neurological disorders with psychiatric manifestations, some early trials using MSCs have reported potential modest benefits, often attributed to immunomodulatory or neurotrophic effects rather than direct neural regeneration (Barba *et al.,* 2017; Volarevic *et al.,* 2018).

However, these results should be confirmed by larger studies. The logistical and operational hurdles for delivering a large number of cells to localized areas in the diseased brain and ensuring that the implanted cells survive and function still represent major obstacles to clinical studies in complex brain disorders.

The field is being cautious stressing the requirement for verified clinical trials on standard platforms. Although the potential of stem cells holds a lot of promise, many so-called treatments are not backed by hard scientific evidence for a wide range of conditions. Work of continuing critical importance is to systematically prove the safety and feasibility of diverse types of stem cells and routes/methods of delivery, the optimal stem cell dosage, and to develop specific biomarkers and outcomes measures to accurately measure potential clinical effects in future larger efficacy trials for neuropsychiatric symptoms.

Future Trajectories and Translational Pathways

Integration with Advanced Technologies (e.g., Gene Editing, Nanotechnology, AI)

Integration of stem cell technology with other new biotechnologies over the field of stem cell therapy for neuropsychiatric disorders will likely occur in the next decade. Technologies for gene editing, such as CRISPR-Cas9, make it possible to edit disease-causing mutations in patient-specific iPSCs before their differentiation and transplantation. This could also result in generating genetically in situ corrected autologous cell re-placement therapies, which hold the promise of mitigating the underlying cause of monogenic neuropsychiatric diseases, or engineering cells to boost survival, differentiation, or secretion of therapeutic factor. Gene editing can also be employed for the integration of genes encoding neurotrophic factors or immune modulatory proteins into stem cells to improve therapeutic efficiency.

Nanotechnology offers potential to enhance the delivery, survival, and targeting of stem cells. Nanomaterials may be designed to contain stem cells or therapeutic components, sheltering them from host environment and promoting transport through biological obstacles of transport, for example, the blood-brain barrier. Nanoparticles can also be formulated for the delivery of genetic material or small molecules to guide stem cell differentiation or to regulate the host tissue niche to promote graft acceptance and function. Biomaterial-based scaffolds that include nanotechnology may offer the 3D support for transplanted cells enhancing survival, guiding differentiation, and promoting integration (Khodayari *et al.,* 2019; Than & Newsome, 2014; Wang *et al.,* 2018).

Neuropsychiatric therapy has entered a new interdisciplinary forefront combining microbiota modulation with early behavioural profiling. Cell-based treatment implementations in personalized protocols that not only correct the gut-brain axis but also facilitate a neuroprotective cell effect may yield even more favourable outcomes by targeting systemic and central neuroinflammatory mechanisms simultaneously. Also, these communication-based stratification tools (such as the ECA) may facilitate therapeutic targeting by defining developmental time windows in which interventions (microbial, behavioural, and stem cell-based) may be most effective (Manaf *et al.,* 2025; Singhania, 2025).

Artificial intelligence (AI) and machine learning will have a major impact in advancing stem cell research and translation. AI can process learned complex patterns from high-content screening of drug candidates on iPSC models to predict efficacy or toxicity. It can further be used to optimize stem cell differentiation protocols by examining large experimental parameters to find the best conditions to produce specific neural subtypes. AI can also be used to analyze complex imaging and electrophysiological data from in vitro models as well as clinical trials to aid researchers in elucidating the mechanisms of action and predicting patient responsiveness. A convergence of these technologies with stem cell biology is anticipated to fuel the generation of more targeted, efficient and safer cell therapies.

Strategies for Targeted Delivery and Precision Therapy

Efficient stem cell therapy for neuropsychiatric disease will require direction of stem cells to defined regions of the brain and matching to individual patient needs (precision therapy). Due to the complicated circuitry of the brain, accurate delivery of cells at specific target site is critical for effective outcome and to prevent off-target effects. Existing approaches are often based on invasive stereotactic neurosurgery. For greater effects in the future, it is likely that future strategies will include innovation in less invasive delivery methods (e.g. focused ultrasound or transient modulation of blood-brain barrier in conjunction with systemic cell administration). On the other hand, somatic cell engineering or targeted carriers such as nanoparticles may enable cells to be directed to the sites of pathology based on molecular guidance.

Precision therapy for stem cells includes selecting the best cell source, cell type, and delivery method for an individual patient based on their diagnosis, genetics, degree of symptomatic impairment, and underlying biology. Patient-specific iPSCs provides unprecedented system to generate patient-specific models to predict responsiveness of therapy or optimal cell product. Genetic analyses of patients could help to identify those most likely to benefit from cell replacement in contrast to patients for whom paracrine support or immunomodulation would be more effective.

These tools will be crucial for optimizing the targeted delivery and monitoring treatment efficacy in a personalized manner by non-invasive tracking of transplanted cells in vivo, monitoring their differentiation, survival and/or integration. Imaging methods to accomplish this, such as MRI, or PET with cell-specific labeling, are being developed. Precision medicine will also depend on the discovery of strong biomarkers that predict response to treatment and track the direct effects of stem cell therapy on disease-relevant neural circuits and symptoms. Integration of targeted delivery with precision strategies guided by advanced diagnostics and computational models will continue to be paramount in realizing the therapeutic potential of stem cells across the complex landscape of neuropsychiatric disorders.

Policy, Regulation, and Funding Landscape

The transition of stem cell treatments from research to clinic is highly influenced by policy, regulation, and funding. Regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are central in assuring the quality, safety, and efficacy of new cell-based products. Regulatory environment of stem cell therapies has been in a state of evolution due to specific considerations surrounding live cell products as opposed to typical drugs. This includes provision of standards in areas such as manufacturing, quality control, preclinical testing and clinical trial design (Gómez-Barrena *et al.,* 2011). This challenging regulatory pathway can only be achieved through careful teamwork among academia, clinicians, industry, and regulatory agencies.

There are several sources of funding for stem cell research, including government funding, private grants, and venture capital. The amount and kind of funding can also affect the speed of research and translation. Public funding of ESC research has been politically debated and restricted in some areas while iPSC and adult stem cell research has generally faced less opposition. Investment into basic research to improve our understanding of stem cell biology and disease pathways, and resource provision to perform meticulous preclinical and well-designed clinical studies, is crucial if progress in the field is to be made (Littman & Abo, 2015). Public-private partnership and international cooperation can facilitate the pooling of resources and expertise to solve the complex problems associated with developing cell therapies for brain diseases.

The morality of stem cell research and therapy is also affected by policy choices. And the International Society for Stem Cell Research (ISSCR) offers guidelines to advance responsible research and clinical trial translation that relate to the use of embryos, genome editing and the generation of human-animal chimeras. And policies must also confront the question of unproven stem cell treatments that many clinics are, in essence, selling directly to patients, enacting stringent regulation to shield vulnerable patients. A supportive and transparent policy environment and strong and effective regulatory processes, combined with continued investment, are essential components for successfully delivering on the potential of stem cell biotechnology to deliver clinically-validated and accessible treatments for neuropsychiatric disorders.

CONCLUSION

Neuropsychiatric diseases represent a significant public health burden, and existing therapeutic approaches are typically inadequate to achieve full remission or treat the underlying pathophysiology. The biotechnology of stem cells promises to transform our understanding of the cause of disease and potentially provide new therapeutic strategies. From the development of patient-specific iPSC lines, to advanced in vitro disease modelling and high-throughput drug screening, to the lofty goal of neural regeneration and repair, stem cells have become the major biotechnological assets for tackling these challenging disorders.

Although enormous opportunity exists, it is difficult to translate experiments to the clinic. Technical barriers for safety of the cells, functional integration into complex neural networks and selection of efficient delivery are to be surmounted. Concurrently we must confront the ethical minefield of stem cell use and tackle economic barriers to accessibility for responsible and equitable translation. Notwithstanding these challenges, developments in preclinical research combined with emerging findings from early clinical studies have set the stage for cautious optimism.

In the future, stem cell treatment for neuropsychiatric diseases will be further combined with gene editing, nanotechnology and artificial intelligence, resulting in a synergistic interaction to optimize treatment strategies with maximal precision and therapeutic efficacy. Remaining needs include further investments in basic research, optimization of regulatory pathways, and to promote international collaboration. Turning the promise of stem cell biotechnology in these devastating diseases into practice will be a process of perseverance, robust scientific validation and ethical utilization yet will ultimately bring new hope to patients who currently have none.

REFERENCES

Barba, M., Di Taranto, G., & Lattanzi, W. (2017). Adipose-derived stem cell therapies for bone regeneration. *Expert Opinion on Biological Therapy, 17*(6), 677–689.

https://doi.org/10.1080/14712598.2017.1315403

Bolte, J., Vater, C., Culla, A. C., Ahlfeld, T., Nowotny, J., Kasten, P., Disch, A. C., Goodman, S. B., Gelinsky, M., Stiehler, M., & Zwingenberger, S. (2019). Two-step stem cell therapy improves bone regeneration compared to concentrated bone marrow therapy. *Journal of Orthopaedic Research®, 37*(6), 1318–1328. https://doi.org/10.1002/jor.24215

Castillo, A., Rodriguez, A., Martín, J., Ginesta, X., Sola, A., & Hotter, G. (2020). Macrophage therapy activates endogenous muscle stem cells and accelerates muscle regeneration. *Research Square* (Research Square). https://doi.org/10.21203/rs.3.rs-53259/v1

Fisher, J. N., Peretti, G. M., & Scotti, C. (2016). Stem cells for bone regeneration: from Cell-Based therapies to decellularised engineered extracellular matrices. *Stem Cells International, 2016*(1). https://doi.org/10.1155/2016/9352598

Fleming, J. N., Nash, R. A., McLeod, D. O., Fiorentino, D. F., Shulman, H. M., Connolly, M. K., Molitor, J. A., Henstorf, G., Lafyatis, R., Pritchard, D. K., Adams, L. D., Furst, D. E., & Schwartz, S. M. (2008). Capillary regeneration in scleroderma: stem cell therapy reverses phenotype? *PLoS ONE, 3*(1), e1452. https://doi.org/10.1371/journal.pone.0001452

Gizaw, M., Faglie, A., Pieper, M., Poudel, S., & Chou, S. (2019). The role of electrospun fiber scaffolds in stem cell therapy for skin tissue regeneration. *Med One*. https://doi.org/10.20900/mo.20190002

Gómez-Barrena, E., Rosset, P., Müller, I., Giordano, R., Bunu, C., Layrolle, P., Konttinen, Y. T., & Luyten, F. P. (2011). Bone regeneration: stem cell therapies and clinical studies in orthopaedics and traumatology. *Journal of Cellular and Molecular Medicine, 15*(6), 1266–1286. https://doi.org/10.1111/j.1582-4934.2011.01265.x

Khodayari, S., Khodayari, H., Amiri, A. Z., Eslami, M., Farhud, D., Hescheler, J., & Nayernia, K. (2019). Inflammatory Microenvironment of Acute Myocardial Infarction Prevents Regeneration of Heart with Stem Cells Therapy. *Cellular Physiology and Biochemistry, 53*(5), 887–909. https://doi.org/10.33594/000000180

Littman, N., & Abo, A. (2015). Proceedings: Using stem cell therapies to reestablish osteogenic capability for bone regeneration. *Stem Cells Translational Medicine, 4*(11), 1247–1250. https://doi.org/10.5966/sctm.2015-0202

Liu, S., Zhou, J., Zhang, X., Liu, Y., Chen, J., Hu, B., Song, J., & Zhang, Y. (2016). Strategies to optimize adult stem cell therapy for tissue regeneration. *International Journal of Molecular Sciences, 17*(6), 982. https://doi.org/10.3390/ijms17060982

Manaf, W., Dileep, N., Manaf, H., Dileep, N., & Liyakath, A. (2025). The Gut-Brain Connection: Investigating the Correlation between Autism Disorder and Gut Bacterium. *American Journal of Life Science and Innovation, 4*(1), 24–34. https://doi.org/10.54536/ajmsi.v4i1.3818

Mazzola, M., & Di Pasquale, E. (2020). Toward cardiac regeneration: combination of pluripotent Stem Cell-Based therapies and bioengineering strategies. *Frontiers in Bioengineering and Biotechnology, 8*. https://doi.org/10.3389/fbioe.2020.00455

Meiliana, A., Dewi, N. M., & Wijaya, A. (2016). Stem cell therapy in wound healing and tissue regeneration. *The Indonesian Biomedical Journal, 8*(2), 61. https://doi.org/10.18585/inabj.v8i2.191

Messina, A., Luce, E., Hussein, M., & Dubart-Kupperschmitt, A. (2020). Pluripotent-Stem-Cell-Derived hepatic cells: hepatocytes and organoids for liver therapy and regeneration. *Cells, 9*(2), 420. https://doi.org/10.3390/cells9020420

Patel, P. (2006). A natural stem cell therapy? How novel findings and biotechnology clarify the ethics of stem cell research. *Journal of Medical Ethics, 32*(4), 235–239. https://doi.org/10.1136/jme.2005.012096

Pinel, L., Mandon, M., & Cyr, D. G. (2019). Tissue regeneration and the epididymal stem cell. *Andrology, 7*(5), 618–630. https://doi.org/10.1111/andr.12635

Rousková, L., Hruška, I., & Filip, S. (2008). Issues and Ethical Problems of Stem Cell Therapy – Where is Hippocrates? *Acta Medica (Hradec Kralove Czech Republic), 51*(2), 121–126. https://doi.org/10.14712/18059694.2017.13

Shi, Y., & Zhang, Y. (2011). Mesenchymal stem cells for cell therapy and tissue regeneration in urology. In *InTech eBooks*. https://doi.org/10.5772/19743

Singhania, R. (2025). Examining Early Communication Profiles in Preschool Children with Autism Spectrum Disorders in Dubai, U.A.E.: A Comparative Analysis of Cognitive, Language and Symbolic Play Abilities. *American Journal of Life Science and Innovation, 4*(1), 8–20. https://doi.org/10.54536/ajlsi.v4i1.2645

Sipp, D., Munsie, M., & Sugarman, J. (2018). Emerging stem cell ethics. *Science, 360*(6395), 1275. https://doi.org/10.1126/science.aau4720

Takahashi, J. (2009). Future of stem cell therapy for neuronal regeneration. *Rinsho Shinkeigaku, 49*(11), 834–836. https://doi.org/10.5692/clinicalneurol.49.834

Tateya, I., & Ito, J. (2003). Stem cell therapy for diseases in the nervous System-A potential for regeneration of inner ear-. *Practica Oto-Rhino-Laryngologica, 96*(9), 831–842. https://doi.org/10.5631/jibirin.96.831

Than, N. N., & Newsome, P. N. (2014). Stem cells for liver regeneration. *QJM, 107*(6), 417–421. https://doi.org/10.1093/qjmed/hcu013

Volarevic, V., Markovic, B. S., Gazdic, M., Volarevic, A., Jovicic, N., Arsenijevic, N., Armstrong, L., Djonov, V., Lako, M., & Stojkovic, M. (2017). Ethical and safety issues of Stem Cell-Based therapy. *International Journal of Medical Sciences, 15*(1), 36–45. https://doi.org/10.7150/ijms.21666

Wang, X., Young, D., Wu, Y., & Loh, X. (2018). Thermogelling 3D Systems towards Stem Cell-Based Tissue Regeneration Therapies. *Molecules, 23*(3), 553. https://doi.org/10.3390/molecules23030553