What will the treatment and support of people with hard to treat psychosis look like in 20 years?
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Introduction

Psychosis is defined by a fundamental impairment in reality testing, characterised by hallucinations, delusions, or both[1]. More broadly, psychosis encompasses significant alterations in perception, thought, mood, and behaviour. Clinical manifestations are typically grouped into positive symptoms, negative symptoms and cognitive impairment. Although psychosis is most commonly associated with schizophrenia-spectrum disorders, it can also arise in affective conditions, substance-induced states and a range of medical illnesses[2]. Despite continued efforts to improve understanding and treatment options for patients with psychosis, approximately 30% of individuals fail to achieve adequate symptom remission following two trials of antipsychotic medication[3,4]. This population is typically described as having treatment-resistant schizophrenia (TRS). However, this terminology risks oversimplification. Poor outcomes do not arise solely from pharmacological non-response. Trauma exposure, substance misuse, medication non-adherence, social adversity, stigma and functional decline all contribute to persistent illness trajectories. The broader construct of hard-to-treat psychosis, therefore, offers a more clinically meaningful framework, recognising the complex interplay of biological vulnerability and psychosocial determinants.

The clinical and economic burden of hard-to-treat psychosis is substantial. Relapse rates remain high, with some studies finding a 81.9% relapse rate in the first 5 years[5]. Treatment-resistant presentations are associated with markedly reduced quality of life and healthcare costs up to ten times greater than non-resistant cases[6]. Over the next 20 years, there will be a conceptual shift where hard-to-treat psychosis will increasingly be reframed not as a failure of dopamine blockade, but as a multidimensional condition requiring coordinated biological, psychological and social intervention. This transformation will not be driven by a single pharmacological breakthrough. Rather, it will emerge through the convergence of advances in biological stratification, digitally augmented psychological therapies, embedded social and vocational rehabilitation, trauma-informed practice and structural reform. This holistic framework appreciates the multiple challenges facing patients with psychosis that cannot be addressed by a singular pharmacological intervention. It will target the challenges patients face day-to-day to improve long-term outcomes and prevent relapse.

Targeted medications

The majority of antipsychotics that are currently used in clinical practise share the same mechanism of action by targeting the postsynaptic dopamine D2 receptors. While such medications are effective in reducing positive symptoms in many patients, their benefits for negative and cognitive symptoms are modest. The severity of negative and cognitive symptoms is strongly associated with poorer functional outcomes, such as psychosocial functioning, employment, and quality of life[7]. Furthermore, antipsychotic medications frequently carry significant side-effect burdens, including extrapyramidal symptoms and metabolic complications such as weight gain, dyslipidaemia and type 2 diabetes. These adverse effects not only compromise physical health but also contribute to treatment discontinuation and relapse. The existing pharmacological approach therefore remains constrained by mechanistic homogeneity and tolerability limitations, resulting in prolonged therapeutic trial and error before effective treatment is identified. Even in those where medication is deemed effective, it does not address some of the most burdensome symptoms that influence how patients are able to function.

The strategy for identifying and investigating novel therapeutic targets will need to shift in the coming 20 years. Advances in genomics, transcriptomics and computational modelling are already challenging the notion of a singular underlying pathophysiology. This presents an opportunity to refresh the approach to drug trials to a more targeted strategy. Increasingly, psychosis appears biologically heterogeneous,

encompassing multiple molecular and neurodevelopmental pathways that converge on shared symptom dimensions. Precision psychiatry seeks to leverage this heterogeneity by tailoring interventions to biologically defined subgroups. Rather than waiting for two failed antipsychotic trials before declaring treatment resistance, future care pathways may incorporate blood-based gene expression profiling, pharmacogenomic risk stratification and inflammatory or endocrine biomarker panels at early stages of treatment. Improving the lives of sub-populations of people with psychosis that share common biological characteristics and are likely to be responsive to a particular compound may be more achievable than aiming to treat the complexities of psychosis as a singular condition with one underlying mechanism.

Recent research has identified blood-based gene expression biomarkers that may improve the management of treatment-resistant psychosis. Investigators identified panels of biomarkers associated with hallucination and delusion severity, as well as risk of future psychiatric hospitalization[8]. Importantly, several biomarkers are modulated by existing treatments, with clozapine showing the strongest molecular alignment, supporting its role as the gold-standard therapy for refractory psychosis. This biomarker-based approach offers a potential shift toward precision psychiatry, enabling objective risk stratification and more targeted treatment selection in individuals who do not respond adequately to standard antipsychotic therapy. Such biological stratification could fundamentally alter prescribing practices. Clozapine is frequently underutilised due to concerns regarding agranulocytosis, metabolic complications and mandatory blood monitoring. In the future, validated biomarker panels may help identify individuals most likely to benefit from clozapine earlier in the illness course while simultaneously predicting vulnerability to adverse effects. This would allow clinicians to initiate effective treatment with greater confidence, potentially reducing years of suboptimal symptom control and recurrent hospitalisation. However, this transition will require robust replication and high predictive validity. Premature clinical implementation without sufficient validation risks misallocation of treatment and erosion of trust in precision approaches.

Beyond biomarker-guided prescribing, recent advances in stem cell modelling opens a new avenue for intervention discovery. Induced pluripotent stem-cell technologies allow patient-derived cells to be reprogrammed into neuronal subtypes implicated in psychosis, enabling investigation of disease-relevant cellular processes. What this might look like can be demonstrated by a study which modelled psychosis using patient-derived stem cells carrying distinct neurexin-1 (NRXN1) mutations[9]. Researchers reprogramed skin cells into glutamatergic and GABAergic neurons, which are implicated in psychosis, by changing the excitatory-inhibitory balance. They demonstrated that both loss-of-function and gain-of-function NRXN1 variants reduced glutamatergic activity and increased GABAergic signalling but via divergent intracellular mechanisms. Crucially, the pathological effects were rescued in a mutation-specific manner, where loss-of-function variants responded to estradiol, whereas gain-of-function variants required gene-targeted DNA constructs to interrupt aberrant protein synthesis. These findings suggest a future in which psychosis treatment may be aligned more closely with underlying molecular mechanisms rather than symptom clusters alone. Complementing this, a 56-day adjunctive estradiol trial in women with schizophrenia identified endocrine biomarkers that predict treatment response[10]. They found that differences in baseline estradiol and follicle-stimulating hormone levels were associated with differential outcomes, supporting the existence of biologically distinct subgroups.

Nevertheless, the clinical translation of such approaches faces significant challenges. Induced pluripotent stem-cell models remain limited by developmental immaturity, constrained network complexity and uncertain ecological validity relative to in vivo cortical systems. Moreover, most cases of psychosis are polygenic and environmentally influenced, limiting the generalisability of findings derived from rare high-penetrance mutations. It is therefore unlikely that personalised stem-cell modelling will become routine clinical practice for all individuals. A more realistic outcome is the development of

biologically stratified prescribing algorithms embedded within electronic health systems, allowing clinicians to match patients to treatment pathways based on aggregated multi-omic data rather than bespoke cellular modelling.

Other treatment avenues

While biological innovation holds promise, medication alone cannot fully address the disability associated with hard-to-treat psychosis. Alongside these innovations, there needs to be a systematic integration of psychological and social rehabilitation into core treatment pathways. Digitally augmented psychological interventions are poised to play a central role in this evolution. Virtual reality (VR) interventions allow for a more immersive experience in which patients can develop skills to manage their psychotic symptoms. This strategy shifts the focus from eliminating psychotic experiences to reducing distress, enhancing coping and restoring agency. For example, cognitive therapy utilising this technology can be used to help patients actively test persecutory delusions while dropping safety-seeking behaviours. *Garety et al* (2024) tested AVATAR therapy to target distressing voices in those suffering from auditory hallucinations[11]. Treatment is focused on trying to reduce voice-related distress and build empowerment in daily life by facilitating a conversation between the voice-hearer and their voices. Voice-related distress improved at 16 weeks but not at 28 weeks, as compared to treatment as usual. The attenuation of effects by 28 weeks suggests that initial symptom relief may not automatically translate into enduring change, underscoring the need for further investigation of mechanisms of maintenance. Subsequent trials should incorporate extended follow-up periods and test structured booster or stepped-care augmentation models to determine how benefits can be sustained in routine practice. Similarly, VR environments allow patients to enter graded social scenarios and directly experience the absence of feared harm to reduce paranoia, which is thought to be maintained by avoidance and defence behaviours[12]. A trial comparing VR-CBTp with standard CBTp showed advantages for VR in reducing safety behaviours, depression, anxiety, and improving self-esteem[13]. All of which are highly relevant to functional recovery in hard-to-treat cases. If these technologies demonstrate sustained efficacy and cost-effectiveness, they may become scalable adjuncts rather than specialist innovations. The broader implication of these technologies is a shift from attempting to eradicate all psychotic experiences to reducing distress and enhancing agency. For individuals with hard-to-treat psychosis, symptom persistence may not equate to therapeutic failure if functional recovery and quality of life improve. In this respect, digital therapeutics may complement pharmacological strategies rather than compete with them. However, the durability of effect, digital literacy, data security and equitable access will determine the extent of their implementation. There is a risk that technologically enhanced interventions could widen disparities if access is restricted to well-resourced settings. Ethical governance and public health investment will therefore be essential to ensure digital augmentation enhances rather than fragments care.

Equally transformative will be the recognition that social rehabilitation is not an optional add-on but a core therapeutic target. Evidence consistently demonstrates that social isolation, unemployment and exclusion predict relapse more strongly than symptom severity alone[14]. Psychotic symptoms may account for only a fraction of illness-related disability, instead social adversity and loss of meaningful roles often drive long-term impairment. To support patients with these struggles, there needs to be a greater focus on social interventions. Structured family intervention for psychosis (FIp) has already demonstrated sustained reductions in relapse, hospitalisation duration, and symptom severity for up to two years following first-episode psychosis, alongside improvements in functional recovery[15]. This highlights the importance of building a support network for patients who can help them through their treatment. Further solidifying this idea, a study showed that individuals with poorer perceived social support have over a threefold increased odds of relapse, underscoring social connectedness as a modifiable prognostic factor[16]. Identifying the type of social support that is most effective in reducing

relapse rates is an important avenue for future research. Another important factor that contributes to relapse is stressful life events. Longitudinal data indicates that exposure to stressful life events after psychosis onset more than doubles relapse risk (HR ≈2.6), with dose-dependent effects on incidence and episode duration[17]. Whilst stress is an inevitable part of life that cannot be prevented, interventions that give patients tools to help mitigate the harmful effects of stressful life events can be developed. This may include support groups, family psychoeducation and stress-monitoring platforms linked to early intervention teams. Intriguingly, a study comparing patients with psychosis to members of new religious movements, who reported similar levels of unusual beliefs but significantly less distress, suggests that the presence of reciprocal, high-quality social relationships may buffer against the emotional impact of delusional ideation[18]. It may be possible to develop programmes aimed at building reciprocal social roles with a focus on employment, volunteering and group memberships. This would provide an environment where patients feel safe and may also help reduce social withdrawal, which is common in patients with psychosis. In 20 years, proactive relapse-prevention infrastructures focused on building social support for patients will become a central part of treatment. In this future model, strengthening belonging and reducing psychosocial adversity will be an important component of a fully integrated biopsychosocial management plan for hard-to-treat psychosis.

Substance use disorders (SUDs) represent one of the most significant and modifiable contributors to hard-to-treat psychosis. Approximately half of individuals presenting with a first episode of psychosis meet criteria for a current substance use disorder, underscoring the extent to which these conditions are intertwined. Substance misuse is associated with a wide range of adverse outcomes, including increased relapse and hospitalisation rates, medication non-adherence, housing instability, legal difficulties and worsening family and social functioning[19,20]. Importantly, individuals with comorbid psychotic and substance use disorders frequently minimise or underreport their use, complicating assessment and delaying intervention. Traditional service configurations, in which addiction and psychosis are treated by separate clinicians or agencies, have consistently demonstrated poor outcomes, with high dropout rates and fragmented care[21]. In the next 20 years, treatment pathways for hard-to-treat psychosis are likely to embed fully integrated dual-diagnosis services within core psychiatric teams. Routine substance use assessment, digital monitoring tools, contingency management programmes, motivational interviewing and cognitive-behavioural interventions delivered within a unified care framework may reduce relapse risk and improve engagement. Rather than conceptualising substance misuse as a peripheral complicating factor, future services may treat it as a central therapeutic target, recognising that addressing addiction is often a prerequisite for stabilising psychosis and achieving sustained recovery. To achieve this, more research is required in identifying which interventions work most effectively for supporting patients with psychosis with co-occurring substance abuse.

A further pillar of future care will be the full integration of trauma-informed frameworks into routine psychosis services. There is an increasing awareness that there is a strong link between post-traumatic stress disorder (PTSD) and psychosis. PTSD symptoms are common in psychotic populations, and approximately 16% of individuals with schizophrenia-spectrum diagnoses meet diagnostic criteria for PTSD[22]. It has been argued that PTSD and psychosis may lie on a continuum of trauma-related reactions, maintained by overlapping cognitive and affective mechanisms[23]. Hallucinations can resemble post-traumatic re-experiencing phenomena, with content often thematically linked to experiences of humiliation, fear or abuse. Historically, clinicians have been reluctant to directly address trauma in psychosis due to concerns about exacerbating symptoms. However, emerging data suggest that treatments currently available for PTSD are effective for psychosis treatment with minimal adaptation required[24]. Techniques such as imagery rescripting (ImRs), which modifies the meaning of traumatic memories by constructing safer outcomes, have demonstrated reductions in voice distress, frequency and trauma intrusions in voice hearers, with sustained effects at follow-up[25]. It is vital that trauma

becomes central to the treatment of psychosis due to the growing body of evidence suggesting that leaving it untreated may hinder recovery. For example, research indicates that childhood trauma is associated with significantly lower rates of positive symptom remission at 12 months and negative symptom remission at 24 months[26]. The study showed a clear dose–response relationship between trauma burden and poorer functional outcomes. Furthermore, it has been shown that many individuals experience deterioration when trauma remains unaddressed. *Campodonico et al (2022)* reported that participants benefited from talking about trauma and that the prolonged lack of opportunities to discuss traumatic events led to a deterioration of their mental health and more negative self-talk[27]. In the next 20 years, trauma-focused therapies are likely to be standard components of early and hard-to-treat psychosis pathways. Although this is a promising avenue, implementation barriers remain, including workforce training, resource allocation and identification of individuals most likely to benefit. Nonetheless, the trajectory toward trauma integration appears strong and aligns with broader movements in mental health toward holistic, person-centred care.

Evidence from Coordinated Specialty Care (CSC) models demonstrates that early, multidisciplinary, and collaborative intervention substantially improves engagement and recovery trajectories[28]. CSC programmes integrate psychiatric medication management, cognitive behavioural therapy, family education and support, and vocational or educational assistance within a unified team structure. In the future, CSC principles may extend beyond first-episode services to persistent and hard-to-treat populations. Where there is also an incorporation of digital relapse dashboards that integrate symptom reports, stress exposure metrics and social connectivity indices into predictive models. Proactive outreach could be triggered when markers of isolation or stress exceed predetermined thresholds, allowing intervention before hospitalisation becomes necessary. Importantly, collaboration between providers, service users, and families fosters a strong therapeutic alliance. Where there is an agreement on shared goals and treatment strategies. A robust provider-rated alliance has been associated with better medication adherence, improved functioning, reduced symptom severity, and greater overall treatment engagement. Giving patients agency in their treatment and putting their needs and wants at the centre is likely to provide better results. In a population where disengagement and relapse are common, giving patients a sense of control over their own recovery will likely reduce relapse rates and non-compliance.

Conclusion

In 2046, a plausible care pathway for an individual presenting with persistent psychosis might begin with a comprehensive biological, psychological and social assessment. Biomarker and pharmacogenomic screening could inform early medication selection, potentially including earlier clozapine initiation where indicated. Trauma history would be assessed systematically, and trauma-focused therapy would be incorporated where appropriate. Social support mapping would identify areas of isolation or vulnerability, prompting family intervention or supported employment referral. Digitally assisted cognitive behavioural modules, potentially delivered via home-based VR systems, would supplement in-person therapy. A secure digital platform would monitor symptom fluctuation, stress exposure and social connectivity, generating predictive alerts for relapse risk. Multidisciplinary teams would respond proactively to early warning signs, reducing reliance on crisis-driven hospitalisation. Early in treatment, patients will also be assessed for substance abuse and receive adequate support for this. Instead of being treated as a separate issue, both psychosis and substance abuse would be targeted simultaneously. The defining feature of this future model would be integration. Biological, psychological and social domains would no longer operate in parallel silos but within a coordinated infrastructure. Hard-to-treat psychosis would be reframed as a dynamic interaction between neurobiological heterogeneity, trauma exposure, stress sensitivity and social context. Treatment would target each domain simultaneously rather than sequentially. The future of hard-to-treat psychosis will therefore not be defined by stronger dopamine

antagonists but by smarter systems of care. Rather than viewing persistent psychosis as evidence of therapeutic failure, clinicians may increasingly recognise it as a signal of unmet multidimensional needs. Addressing those needs through coordinated biological, psychological and social intervention offers the most promising path toward sustainable recovery in the decades ahead.

Figure 1: Future treatment of hard-to-treat psychosis (OpenAI, 2026)

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