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Schizophrenia® & Psychosis Action Alliance

Schizophrenia Medicines in Jeopardy

Inflation Reduction Act provisions hit the schizophrenia community especially hard, threatening treatment innovation for vulnerable patients already stuck with decades-old medicines.

Schizophrenia is a serious, chronic brain disease that affects more than 2.5 million people in the United States.[1] Yet, in a world where new treatments and even cures are being developed for many diseases, most people with schizophrenia are forced to rely on decades-old medicines that can cause debilitating side effects.

A few recent bright spots have signaled a potential turning point for people with this devastating, difficult-to-treat disease. Despite the challenging research and development (R&D) environment, innovative medicines with novel mechanisms of action are emerging, and a new class of treatment has been approved for the first time in more than 30 years (see *The First New Treatment in Decades*, page 2).[2] However, those bright spots have been overshadowed by key provisions in the recently enacted Inflation Reduction Act (IRA). While the IRA was established with the goal of reducing medicine prices, it has created new barriers for this already vulnerable patient population by further jeopardizing patient access and threatening to shut down future treatment innovation.

A disease with massive treatment gaps

Only about 5% of people with schizophrenia receive the evidence-based treatment practices that lead to optimal outcomes—and **nearly half receive no treatment at all**.[3,4] Even when people with schizophrenia are able to access treatment, the choices are often limited to drugs that do not work for all people and can leave some symptoms unaddressed.[5] When they do help, they can cause debilitating side effects such as considerable weight gain, diabetes, heart disease and movement disorders.[6] One such movement disorder, tardive dyskinesia, can cause uncontrolled facial or body movement that severely impacts the quality of life not only physically but psychologically, socially and professionally.[7]

The First New Treatment in Decades

For the first time in 30 years, in 2024, the U.S. Food and Drug Administration (FDA) approved a drug that takes a novel approach to treating schizophrenia symptoms while minimizing the side effects that can be associated with current treatments.

- This new treatment targets proteins in the brain known as muscarinic receptors. This novel mode of action provides a more comprehensive therapeutic effect than other schizophrenia treatments.[8] In clinical trials, the treatment not only improved the hallmark symptoms of schizophrenia, such as delusions and hallucinations, but also led to indications of improved cognitive function.
- The unique mechanism of action avoids the burdensome side effects associated with other antipsychotics. This offers new hope for people who have not responded to existing therapies or have struggled with intolerable side effects.[8]
- The new medicine also is being studied for treating patients with Alzheimer's-related psychosis, and there are plans to evaluate it for other neuro-psychiatric disorders.[9]

There are multiple reasons for these massive treatment gaps. Diagnosis can take years, as people often only enter care at crisis points, such as through hospitalizations or law enforcement encounters.[10,11] Social determinants of health, stigma and symptoms such as anosognosia—which prevents people from understanding they have the disease—further delay access to treatment.[12,13,14] Payers may also restrict access to therapies, which can cause delays or rejections of critically needed medicine (see *Deep Dive: Access restrictions pose significant health threat to people with schizophrenia*, page 9). The inadequate treatment of schizophrenia contributes to severe consequences, including neurological damage, worsening symptoms and an average lifespan that is 15 years shorter than that of the general population (see *Deep Dive: The devastating human and societal toll of schizophrenia*, page 7).[10,15]

Developing new treatments for schizophrenia is difficult, as there are still many knowledge gaps in what causes the disease and some workings of the central nervous system (CNS) remain notoriously elusive. Medicines used to treat mental illness have the longest clinical development timelines and some of the lowest odds of reaching FDA approval. Only about one in 20 medicines that target the CNS is successful in clinical trials—half the average success rate of all medicines.[16,17] When CNS drugs fail, they unfortunately tend to do so in late-stage trials and after significant financial investment.[18]

All of these factors create enormous financial risk for drug developers and thus have deterred investment and innovation. In fact, research programs in mental illness among large pharmaceutical companies fell by as much as 70% between 2006 and 2016, with many companies switching their focus to other therapeutic areas.[19] Despite the need for novel treatment approaches for mental illnesses such as schizophrenia, a significant unmet need remains due to these R&D challenges.

> **"I'm extremely stressed out feeling the weight of the world on my shoulders. I've never been on an antipsychotic medication that works for these delusions. I dream of being on one that works."**

Report to FDA: *Reimagine Schizophrenia: Transforming How We Are Treated, Function and Thrive.*

IRA imperils cornerstone of schizophrenia treatment, threatens innovation for vulnerable patients

After decades of R&D challenges and many failed drug candidates, novel treatments are in the pipeline for schizophrenia, offering hope to the millions who suffer from the disease (see *Deep Dive: New treatments are critical for the future of people with schizophrenia*, page 11). But just as this promise is becoming a reality, IRA provisions have been enacted that directly impact the type of medicines most likely to work for people with schizophrenia.

The IRA established the Medicare Drug Price Negotiation Program (the Program). Under this Program, the government can set prices for eligible medications in Medicare well before the treatments would otherwise typically face generic or biosimilar competition. This shortens the timeframe in which drug developers can earn revenues on medicines to justify their extensive R&D investments—dramatically shifting how drug developers make future investment decisions. Pharmaceutical companies will now be forced to make tough decisions about whether it is feasible to invest in therapeutic areas that may be disproportionately impacted by the Program.[20]

For example, therapeutic areas that rely heavily on small-molecule medicines and R&D that occurs after initial FDA approval are essential for advancing new treatments for patients—yet they are particularly disadvantaged under the IRA. Diseases that have high levels of medicine use under Medicare are also disproportionately impacted. **Schizophrenia is a therapeutic area that falls under every one of these high-risk categories:**

1. **There is significant utilization of schizophrenia medicines in the Medicare program.** Fewer than one in five people with schizophrenia are able to maintain paid employment, and many are supported by Social Security Administration programs due to their disability.[21] In most states, these patients also qualify for Medicaid and dual eligibility for benefits under Medicare, meaning that many beneficiaries receive drug coverage under Medicare Part D.[22] The medicines selected for price setting under the IRA are chosen in large part based on Medicare spending levels. Given the significant utilization of antipsychotic medications in this patient population and associated levels of Medicare spending, the Center for Medicare and Medicaid Services (CMS) announced in January 2025 that it has selected two schizophrenia-related medicines for price setting starting in 2027.[23]

Greater access restrictions under the IRA may result in additional barriers to treatment for people with schizophrenia.

Changes to the Part D program under the IRA are expected to cause Part D insurance plans to restrict access to medicines to manage increased cost liabilities. Although the IRA requires Part D plans to cover medicines that are selected for price setting, it does not prevent them from imposing more stringent access barriers, higher cost-sharing or more restrictive medication coverage on beneficiaries. A recent survey showed that as a result of the IRA, nearly 90% of payers will increase utilization management and pare down medication coverage, and 78% of payers are expected to create more stringent utilization management for new medicines.[24] For people with schizophrenia who already face significant utilization management restrictions (see *Deep Dive: Access restrictions pose significant health threat to people with schizophrenia*, page 9), this would make the barriers to treatment even higher, risking the health of millions of people with this brain disease.

2. **Small-molecule medicines are the cornerstone of schizophrenia treatment.** Small molecules are crucial to the treatment of mental illnesses such as schizophrenia due to their unique ability to cross the blood-brain barrier and reach disease targets inside the brain.[25] But small-molecule medicines can be selected for price setting as early as seven years after FDA approval—four years earlier than other medicines face under the Program, and far shorter than the 13-14 years these medicines average on the market before facing generic competition.[26]

   Given the schizophrenia community's reliance on small-molecule medicines, the IRA's price-setting framework is expected to have an especially negative impact on these already marginalized patients. In fact, in a survey of pharmaceutical companies, 63% of companies said that under the reduced small-molecule timeframe established under the IRA, all else being equal, they expect to shift R&D investment away from small-molecule medicines toward biologic medicines.[27] This could leave the schizophrenia community with outdated treatments with limited efficacy and debilitating side effects.

3. **The schizophrenia patient community depends on post-approval R&D to advance new treatments.** R&D doesn't stop after a medicine is FDA approved. Pharmaceutical companies often continue to research and develop these medicines to identify new uses for different diseases or patient populations. This post-approval R&D has proven instrumental in advancing new options for people with schizophrenia and other neuropsychiatric conditions (see *Post-Approval R&D Led to Treatment for Children with Schizophrenia*, right).

   The shortened IRA timeframes for companies to conduct post-approval R&D—especially for small-molecule medicines—jeopardize future treatments. Companies may find this shortened timeline economically infeasible. In a survey of pharmaceutical companies, 95% said that when facing hard investment choices, they expect to develop fewer new uses of already-approved medicines.[27] For patient communities that rely on post-approval R&D to advance new uses of existing treatment options for other mental illnesses, this shift in drug development may reduce potential new medicines.

Post-Approval R&D Led to Treatment for Children with Schizophrenia

Lurasidone is an atypical antipsychotic treatment that was FDA approved in 2010 for adults with schizophrenia. Post-approval R&D then led to several additional approvals:[28,29]

- 2013: Approved for use in adults with depressive episodes associated with bipolar depression.
- 2017: Approved for use in adolescents with schizophrenia (ages 13-17).
- 2018: Approved for use in pediatric patients (ages 10-17) with bipolar depression.

The clinical development program for this treatment involved many years of research, significant financial risk and investment to obtain FDA approval for the initial use as well as each subsequently approved use. Moving forward, this development program may be deemed infeasible to pursue due to the limited timeframe to conduct post-approval R&D under the IRA's price-setting framework for small-molecule medicines, the R&D challenges and the low probability of success in this therapeutic area.

4. **The schizophrenia patient community also relies on post-approval R&D to advance new dosage forms and formulations.** People with schizophrenia rely on long-acting medicine formulations to improve their treatment adherence, which can be challenging for people with this brain disease (see *Long-Acting Medications*, below). These formulations are often developed under entirely different clinical development programs many years after the initial approval of the oral dosage form and typically are submitted to the FDA and approved under separate drug applications. But due to CMS's interpretation of drugs eligible for price setting under the Program, medicines containing the same active ingredient or moiety will be treated as the same drug for the purposes of price setting, regardless of when they were developed or approved. So if a pharmaceutical company developed a long-acting version of an existing once-daily antipsychotic medication that reduced dosing to once every six months, that new drug product may be price set along with the original formulation—even if it was FDA approved many years after the original formulation.

   This new reality limits incentives to invest in R&D for new formulations of existing medicines. Jeopardizing future long-acting medicines could take away the improved health outcomes for patients and healthcare system savings that can be achieved with these medicines.

Collectively, the IRA's price-setting provisions and CMS's implementation of the Program undermines the development of future treatments to fill the massive treatment gaps faced by people with schizophrenia.

Long-Acting Medications

For people with schizophrenia, medicine adherence is a top priority, because it decreases disease exacerbations, hospitalizations and risk of relapse.[30] However, studies show that nearly half of people treated for schizophrenia outside of psychiatric hospitals do not take daily oral medications appropriately.[31,32] Today, long-acting medications (LAMs), which are antipsychotics given as injections, can be administered as infrequently as once every six months depending on the medication. Real-world use studies demonstrate that LAMs increase medicine adherence and improve outcomes, leading to a lower likelihood of hospitalization and fewer emergency room visits.[33]

LAMs not only improve health outcomes for people with schizophrenia, they also help reduce long-term healthcare costs for patients and the health system. Among Medicaid beneficiaries with schizophrenia, improved adherence associated with LAM antipsychotics generated annual net savings of up to $3.3 billion, or $1,580 per patient per year, driven by lower rates of hospitalization, outpatient care and criminal justice system involvement.[34] Despite the benefits of LAMs and the human and societal benefits these innovations provide for the treatment of schizophrenia, they are underused—in part because of access barriers. Survey data show that fewer than one in five people with schizophrenia use a LAM and fewer than one in three outpatient mental healthcare providers prescribe LAMs.[35,36]

Conclusion: Solutions Urgently Need to Advance Schizophrenia Treatment and Protect Patients from IRA's Unintended Consequences

The schizophrenia community has been marginalized for decades; now, people with this brain disease stand to suffer even more as the IRA endangers the promise of new schizophrenia treatments. The significant unmet need and treatment access barriers already have disastrous consequences and impose a significant burden on patients, caregivers, our healthcare system and society—including a 15-year shortened life expectancy, heightened rates of homelessness and incarceration and significant economic costs.[37] The societal cost of schizophrenia reflects not only an economic loss, but also a moral failure of a healthcare system that has neglected one of our most vulnerable populations (see *Deep Dive: The devastating human and societal toll of schizophrenia*, page 7).

Just as promise in the treatment R&D pipeline has emerged, the IRA is imposing new burdens. The law's price-setting framework undercuts the development of the small-molecule medicines people with schizophrenia depend on and shortens the timeline for investing in R&D after initial FDA approval—disproportionately discouraging the R&D investments in schizophrenia that are needed to advance treatment progress for this patient community. The IRA also is expected to increase the risk that Part D insurance plans will impose utilization management restrictions on medicines, which could worsen the access barriers many people with schizophrenia already face.

For the 2.5 million people living with schizophrenia in the United States, future treatment innovation is a matter of survival and dignity. They deserve treatments that effectively manage their symptoms without debilitating side effects. They deserve treatments that allow them to recover, return to school or work, develop meaningful relationships, contribute their skills to their communities and experience meaningful lives.

Policies in the IRA have unintended consequences that may jeopardize future treatment options for this vulnerable community. Future progress against mental illnesses such as schizophrenia requires policies that recognize the importance of supporting R&D that advances the next generation of treatments and gives people a chance to recover and thrive.

The devastating human and societal toll of schizophrenia

HUMAN IMPACT

Schizophrenia significantly impairs thinking, perception and daily functioning. A hallmark of the disorder is psychosis symptoms, such as hallucinations, delusions and disorganized thinking or speech. People with schizophrenia can also suffer from antisocial behavior and cognitive problems such as issues with attention, concentration and memory. Additionally, schizophrenia is associated with suicide, cardiovascular disease, substance use disorder, metabolic syndrome, obesity and accidental death—reducing a person's lifespan by 15 to 20 years.[15,38]

> "On his best days, [my son] socializes with people and can carry on a simple, uncomplicated conversation. On the most difficult days, he chants offensive words over and over and can't leave his bed."

Report to FDA: *Reimagine Schizophrenia: Transforming How We Are Treated, Function and Thrive.*

People with schizophrenia often are diagnosed between their teens and early 30s, just when they may be entering the most pivotal phase of their lives, such as starting college or beginning a promising career. The symptoms are often so devastating that they can derail a person's life.[39] Compounding this suffering is the fact that schizophrenia is one of the most stigmatized illnesses in the United States, and many with the disease are often misunderstood.[40,41] Internalized shame is common. This self-stigma can cause lower self-esteem, increased psychiatric symptoms, a reluctance to seek help and reduced likelihood of staying on treatment.[42,43]

Without early intervention, people with schizophrenia are at significant risk of homelessness, incarceration, substance use and disability.[44] Approximately one in five homeless people has schizophrenia. Almost half of people with schizophrenia have contact with law enforcement or the judicial system annually, and one in 12 people who are incarcerated in the United States has a psychotic disorder such as schizophrenia. Unemployment rates for people with severe mental illnesses such as schizophrenia are estimated to reach 70%.[45,46,47,48]

> "I'm afraid the cognitive impairment is going to get worse over time and when I'm older, I won't be able to take care of myself as well as I can now… I can take care of myself pretty well on my best days, but on the worst days, I need to be hospitalized for suicidal ideation or just paranoia."

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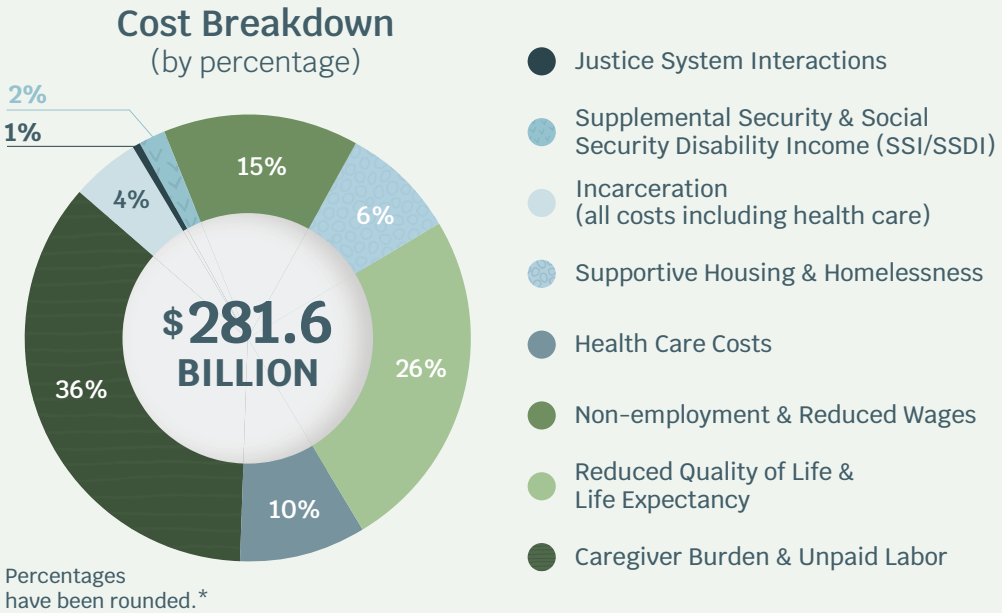
Treatment inequities are pervasive and can lead to progressive cognitive decline.[21] Significant racial disparities also exist. For example, pathways to care for Black individuals with schizophrenia are generally more convoluted and coercive than those of White individuals, including more frequent emergency room visits, involuntary hospitalizations and police encounters.[49,50]

SOCIETAL AND ECONOMIC IMPACT

More than 2.5 million people in the United States are living with schizophrenia, imposing a substantial burden on those with the illness, their caregivers, the healthcare system and society. Managing the complex symptoms and conditions associated with schizophrenia and its treatment comes with a significant price tag—one that is disproportionately high compared with the prevalence of the disease:[1,51]

- Schizophrenia costs the United States more than **$281.6 billion every year**. Only about 10% of this is due to direct healthcare costs; the rest results from the downstream effects of inadequate treatment (e.g., incarceration and homelessness).[37] Indirect costs also stem from factors such as unpaid caregiver time and lost caregiver wages, patients' inability to work and shortened life expectancy. The cost of rehospitalization due to treatment nonadherence is estimated at roughly $1.5 billion per year.[52]
- For each person diagnosed with schizophrenia at age 25, the **total lifetime cost to the economy is about $3.8 million, or $92,000 per year**.[37]
- Law enforcement, judicial and prison systems often shoulder the costs of caring for people with schizophrenia, as those living with the disease are more likely to be victims of crimes or arrested for wrongdoing.[53] **In 2020, the estimated cost to local and state governments totaled over $2.3 billion in law enforcement encounters and judicial system costs and $14.5 billion in incarceration costs.**[37]



Access restrictions pose significant health threat to people with schizophrenia

Antipsychotic medicines are critical for improving the health and lives of people with schizophrenia, but they have become a primary target of payer efforts to contain prescription drug costs.[54] While access to treatment can reduce the significant burden of this disease—including dangerous relapses and expensive hospitalizations—payers often restrict patient access to therapy through a strategy called utilization management. The goal of this strategy is to reduce prescription drug costs for payers—but while it may save them money in the short term, it can cause physical harm to people with the disease and result in much higher healthcare and societal costs down the road.

Antipsychotics are among the most frequently targeted classes of drugs for utilization management.[54] This includes prior authorization, where approval from the health insurer is required before a prescription can be filled, and step therapy, in which a person must "fail" on one or more medications before trying another. Utilization management can negatively influence clinical decisions or force patients to try several different treatment regimens that don't work for them, which can lead to non-adherence or discontinuation of treatment.[55]

Importantly, restrictive access policies can cause delays or denials of critically needed medicine. One study showed that approximately one in three patients with schizophrenia prescribed an antipsychotic had the initial prescription rejected by a payer. During the following six months, nearly half of these patients did not receive the medication from the original prescription, and over 10% never received **any** antipsychotic medicine.[56]

In this patient population, stigma and discrimination can already reduce the likelihood of seeking treatment; even a seemingly minor access barrier can lead to patients going untreated and becoming even more ill.[55]

Policies that restrict access to treatment are particularly harmful to people suffering from mental illnesses, causing negative outcomes such as emergency room visits, hospitalizations, homelessness and criminal justice involvement.[44,57] **Utilization management also results in higher costs to the healthcare system and economy overall.** Based on studies of state Medicaid programs:

- People with schizophrenia who are subject to coverage restrictions are more likely to be hospitalized, have 23% higher inpatient costs and experience 16% higher total medical costs.[57]
- Prior authorization requirements for schizophrenia medication are associated with a 22% increase in the likelihood of imprisonment for people with schizophrenia.[58]

Given the high cost of incarceration alone, these increased costs to the healthcare and criminal justice systems negate any savings created by utilization management.[57] Restrictive utilization management policies not only fail to achieve their cost-saving objective, but also can cause great harm to patients by blocking them from the treatments they need to manage their brain disease.

Utilization management also undermines recent progress in R&D by restricting access to breakthrough treatments. This jeopardizes the potential of recently approved medicines and those in the R&D pipeline to improve symptom management and outcomes for patients (see *Deep Dive: New treatments are critical for the future of people with schizophrenia*, page 11). Newer, brand-name medications are more likely to require prior authorization or step therapy before a patient can use them; this is especially damaging for people with schizophrenia for whom older medicines haven't worked.[59,60]

New treatments are critical for the future of people with schizophrenia

The causes of schizophrenia are multifaceted due to the complex interplay between multiple genes and environmental factors.[61] This complexity means that many people with schizophrenia do not respond to available antipsychotic treatments.[62] Many patients must try many medicines before they find one that meets their complex needs and can be tolerated. Many never find one.[61] Even when they are effective for some symptoms, treatments may not work on other debilitating symptoms. Existing medicines can also cause serious side effects, such as weight gain, metabolic disturbances and movement disorders. One such movement disorder, tardive dyskinesia, can cause uncontrolled facial or body movement that severely impacts the quality of life, not only physically but psychologically, socially and professionally. Such side effects can result in treatment nonadherence and further reduce the effectiveness of the medication.[6,7,61] As a result, there is a significant unmet need for this vulnerable population.

> **"The medications never fully helped my son, and the side effects were atrocious, including massive weight gain, tardive dyskinesia, flat affect, cognitive decline and an inability to stay awake during school hours and do his homework."**
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> Report to FDA: *Reimagine Schizophrenia: Transforming How We Are Treated, Function and Thrive.*

A PROMISING PIPELINE PROVIDES HOPE

Despite the significant challenges, recent progress offers hope to people struggling with this debilitating disease. A recent analysis identified nearly 35 medicines in development for treating schizophrenia, including next-generation medicines that target novel proteins in the brain. These advanced treatments target receptors that are unaddressed by currently available treatments.[63,64]

Among these long sought-after, difficult-to-develop next-generation medicines are muscarinic receptor agonists, a class of medicines that offers enormous potential to address the unmet needs.[65] These medications alleviate a broader range of schizophrenia symptoms while avoiding many of the side effects associated with older antipsychotics. The first of these medications was approved in 2024 (see *The First New Treatment in Decades*, page 2).

The promise of these next-generation medicines has ignited an expansion of R&D in schizophrenia, and several other drugs under investigation target novel pathways.[63] This offers tremendous hope to those who continue to lack effective treatment options or cannot tolerate existing therapies.

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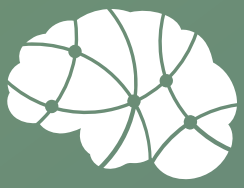

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