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The Pharmacologic Treatment of Schizophrenia–2021

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Schizophrenia is a chronic psychotic disorder with typical onset in early adulthood and a lifetime prevalence of approximately 1%. In addition to the hallmark symptoms of psychosis (delusions, hallucinations, disordered thinking), individuals may experience negative symptoms (apathy, loss of emotional expression) and cognitive deficits. In the past, people with schizophrenia often were confined life-long to psychiatric hospitals; however, the introduction of effective antipsychotic drugs, starting with chlorpromazine (Thorazine) in 1954, followed by the federal Community Mental Health Act of 1963 resulted in deinstitutionalization of an estimated 92% of hospitalized patients by 1994. Although outpatient treatment has been largely successful in allowing people with schizophrenia to live in the community, a shortage of treatment and rehabilitation services and housing, combined with reluctance of some to accept services, has contributed to high rates of homelessness and incarceration among those with schizophrenia in the US.

Supplemental content

First-Generation Antipsychotics and Clozapine

After the introduction of chlorpromazine, additional "first-generation" antipsychotic agents were developed (Supplement); these agents did not differ in efficacy and were found to share dopamine D_2 receptor antagonism in common, along with associated adverse effects of parkinsonism, akathisia (motor restlessness), tardive dyskinesia (potentially irreversible choreiform movements), and hyperprolactinemia. The lack of options for people who did not respond to first-generation antipsychotic drugs led to the delayed development of clozapine, which was derived in 1958 from the antidepressant imipramine and subsequently found to have unique antipsychotic efficacy, but was abandoned due to the adverse effect of agranulocytosis, which occurs in about 1% of patients. Clozapine was approved by the US Food and Drug Administration (FDA) in 1990 for treatment-resistant schizophrenia with mandated monitoring of white blood cell counts. Clozapine improves refractory psychosis in up to half of patients, reduces suicidality, and is virtually free of neurologic adverse effects and prolactin elevation.

Second-Generation Antipsychotics

The clinical benefits of clozapine prompted renewed efforts to develop novel antipsychotics. An early hypothesis to explain the unique efficacy of clozapine posited a favorable ratio of serotonin 5-HT_{2A} antagonism to D_2 antagonism. This model produced a series of "second-generation" antipsychotics (Supplement), starting with risperidone in 1993, that displayed reduced neurologic adverse effects, but without clearly better efficacy compared with first-generation agents. Olanzapine, a chemical analogue of clozapine, was found to have intermediate efficacy between clozapine and other antipsychotic agents in the National Institute of Mental Health–funded CATIE study, whereas network meta-analyses have found a small efficacy advantage associated with olanzapine, risperidone, and amisulpiride (which is not approved in the US). The use of clozapine and olanzapine has been limited by adverse effects of weight gain and insulin resistance. Starting with aripiprazole in 2002, 3 D_2/D_3 receptor partial agonist antipsychotics have been approved by the FDA; these additional second-generation agents also reduce risk of neurologic adverse effects. In total, 10 second-generation antipsychotics are available in the US, all of which have similar efficacy but differ meaningfully in adverse effect profiles.[1]

Several first- and second-generation antipsychotics are available in long-acting injectable formulations, with injection intervals ranging from 2 to 12 weeks. Because unrecognized nonadherence with oral medication may complicate treatment, these long-acting preparations are expected to improve outcomes. Nonadherence may result from several factors, including distressing adverse effects, the absence of shared decision-making, and impaired insight in some patients. Evidence from administrative database studies has identified a reduced risk of relapse with long-acting injectable agents, but clinical benefit has not been observed consistently in randomized clinical trials, possibly because study participants may be more adherent than patients treated under typical clinical conditions.

Psychosocial Interventions

The second-generation antipsychotics are effective in about 60% of patients, with a number needed to treat of 6 for acute psychosis and of 5 for the prevention of relapse.[2] Among responders, some patients are able to function independently, whereas others remain disabled despite successful control of their psychotic symptoms. This residual disability has been attributed to negative symptoms and cognitive deficits, which are much less responsive than psychosis to available drug treatments. The persistence of disability and reduced quality of life and the challenges of poor adherence with medication have necessitated the delivery of a broad range of evidence-based psychosocial services, including cognitive behavioral therapy; family psychoeducation; social skills training; assertive community treatment; and assistance with work, education, and housing. This enriched menu of rehabilitation services, when combined with optimal pharmacotherapy in individuals early in the course of illness, has demonstrated substantial benefit across a broad range of outcomes compared with treatment as usual.[3]

Controversies in Drug Treatment

Because delay in initiating treatment has been associated with poor outcomes, it has been hypothesized that untreated psychosis may have persistent detrimental effects.[4] This hypothesis has not been rigorously tested because placebo-controlled trials of long duration are generally considered to be unethical; withholding of effective treatment may prolong the discomfort and risks associated with psychosis while potentially worsening long-term outcomes. Several alternative explanations may account for the association between treatment delay and poor outcome, including the greater likelihood that medication will be initiated more rapidly in individuals with a form of illness with a good prognosis (eg, acute onset in the setting of good premorbid function) and that previous analyses may have been confounded by "lead-time bias," in which a deteriorating course of illness that is refractory to medication produces apparently worse outcomes after a delay in treatment initiation, falsely attributing the worse outcome to the treatment delay.[5]

The long-term effect of medication is also a topic of debate.[4] An observed association between cumulative antipsychotic exposure and reduced brain volume has been interpreted as evidence that medication

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may be neurotoxic, but an alternative explanation that clinicians prescribe higher doses to those with poor-prognosis illness cannot be ruled out.[4] If long-term antipsychotic treatment reduces gray matter brain volume, the functional consequences remain unclear. Whether some might benefit from medication discontinuation is a topic of current research; preliminary evidence suggests that as many as 20% of patients with early schizophrenia who experience remission may benefit from careful tapering and discontinuation of medication,[6] but risk of relapse can be serious, including incarceration, self-harm, and diminution of subsequent treatment response. The current recommendation is to initiate comprehensive treatment as early as possible and avoid relapse, while minimizing antipsychotic adverse effects as much as possible.[4]

Alternative Strategies to Improve Clinical Course

A "clinical high-risk" or "prodromal" stage precedes schizophrenia in some patients and is characterized by functional decline and low-level or transient psychosis; this early stage has been targeted by investigators in the hope that progression to full psychosis, which occurs in up to 36% of cases, can be averted.[7] Despite efforts to identify biomarkers and biological mechanisms associated with illness progression, no pharmacologic or psychosocial intervention has demonstrated superiority over usual treatment for reducing rates of transition to psychosis or disability associated with the clinical high-risk syndrome, although some evidence suggests a role for cognitive behavioral therapy.[8]

Another strategy to improve treatment outcomes has focused on reducing heterogeneity by identifying meaningful biological subtypes. More than 100 common risk alleles have been identified with very small effects, in addition to rare copy number variants with larger effects. Many molecular pathways have been implicated, including modulators of neurodevelopment, immune response, synaptic integrity, and energy metabolism. Although molecular targets based on individual risk alleles have not yet produced therapeutic advances, a positive polygenic risk score based on many risk alleles identifies individuals at increased risk and may predict treatment response.[9] Other strategies to reduce heterogeneity have used the examination of specific brain circuits using neuroimaging and the identification of "endophenotypes," which are readily measurable components of brain dysfunction characteristic of schizophrenia. The National Institute of Mental Health formalized a matrix for examining 6 domains of brain function relevant to all psychiatric disorders according to genetic, physiological, behavioral, and self-report assessments informed by neurodevelopmental and environmental factors known as the Research Domain Criteria system. Consistent with the Research Domain Criteria approach, newly emerging data-driven computational approaches may ultimately be necessary to achieve a precision medicine approach to this complex and heterogeneous neurodevelopmental disorder.

Current Drug Development

Several models currently guide treatment development for schizophrenia, including the classic model of dysregulated dopamine transmission, hypofunction of glutamatergic *N*-methyl-D-aspartate receptors, dysregulation of excitatory/inhibitory balance, immune dysfunction, and aberrant dendritic pruning, but no single model explains this complex syndrome. Traditional animal models for schizophrenia that target individual receptor subtypes or disrupt neurodevelopmental processes have been poorly predictive for drug discovery. In a study published in 2020, a novel behavioral approach in mice designed to identify molecules that mimic the effects of antipsychotic drugs led to the development of an agent with agonist activity primarily at the trace amine–associated receptor 1 and serotonin 5-HT_1 receptors that demonstrated efficacy for psychosis and negative symptoms without significant neurologic or metabolic adverse effects in an initial phase 2 trial.[10]

Conclusions

Available treatments for schizophrenia have transformed the lives of people with schizophrenia, allowing most to live in the community and many to function independently. However, considerable unmet needs remain because many people experience symptoms and cognitive deficits refractory to available treatments, and adverse effects of medication are common. Despite the rapidly advancing neuroscience of psychiatric illness, treatment development has lagged, in part due to a scaling back of investment by industry and federal funding sources. The examples of clozapine and, most recently, the novel trace amine–associated receptor 1 target suggest that meaningful therapeutic advances are quite possible and should be pursued while more complex neurodevelopmental and molecular models are developed.

ARTICLE INFORMATION

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