The Complexities of Schizophrenia Clinical Trials:

Diagnosis, Management and Research

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Introduction

Schizophrenia is a chronic, severe mental disorder characterized by profound disruptions in thinking, affecting language, perception, and sense of self.

Schizophrenia significantly impairs an individual's ability to function in daily life and often leads to considerable personal, social, and occupational challenges. The disorder typically manifests in late adolescence or early adulthood, with a slightly earlier onset in males than females.

The understanding of schizophrenia has evolved significantly since it was first described. The term "schizophrenia" was coined by Eugen Bleuler in 1911, replacing the earlier term "dementia praecox" used by Emil Kraepelin. Bleuler emphasized the disorder's fundamental symptoms of altered association, affect, ambivalence, and autism, alongside more episodic disturbances like hallucinations and delusions.

Over the decades, advances in neurobiology, genetics, and neuroimaging have transformed our understanding of schizophrenia from a purely psychological disorder to one with substantial biological underpinnings. Early theories centered around psychodynamic and psychosocial causes have given way to a more integrated biopsychosocial model, recognizing the interplay of genetic, neurochemical, and environmental factors.

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Key Characteristics and Contributing Factors

Key Characteristics

Positive Symptoms

- **Hallucinations** are sensory experiences without an external stimulus. The most common type of schizophrenia is auditory hallucinations, where individuals hear voices that aren't present.
- **Delusions** are firmly held false beliefs that remain unshaken despite evidence to the contrary.
- **Disorganized thinking** is often reflected in speech. Individuals may exhibit loose associations, where thoughts jump from one topic to another with little coherent connection.
- **Disorganized behavior** encompasses a range of actions that are inappropriate for the situation or lacking in goal-directed purpose.

Negative Symptoms

- These are deficits in normal emotional and cognitive functions, such as reduced emotional expression (affective flattening), lack of motivation (avolition), inability to experience pleasure (anhedonia), and decreased speech output (alogia).

Cognitive Deficits

- Individuals may experience impairments in memory, attention, executive function, and critical thinking skills.

Contributing Factors

Biological Factors

- Schizophrenia has a strong genetic component, with heritability estimates around 80%. The risk of developing schizophrenia increases if a first-degree relative, such as a parent or sibling, has the disorder. Neurochemical imbalances, particularly involving dopamine, glutamate, and serotonin, are implicated in the pathophysiology of schizophrenia.

Psychological Factors

- While less emphasized than biological factors, psychological stressors can trigger or exacerbate the onset of schizophrenia. Traumatic experiences, particularly during childhood, can increase vulnerability to the disorder.

Environmental Factors

- Environmental factors play a critical role in the development and exacerbation of schizophrenia. Prenatal exposure to infections, malnutrition, or stress increases the risk of developing the disorder. Urban upbringing has been associated with a higher incidence of schizophrenia, due to increased exposure to stress, pollution, and social adversity.

Prevalence, Trends, and Market Analysis

Prevalence and Trends

Schizophrenia affects approximately 24 million people worldwide, representing about 0.32% of the global population. In the United States, around 3.5 million individuals are affected. The disorder typically manifests in late adolescence or early adulthood, with men often showing symptoms earlier than women (WHO, 2022; NIMH, 2023).

Over the past decade, schizophrenia prevalence has remained stable. However, demographic changes, such as population growth and aging, suggest a potential increase in the absolute number of cases. Analysis of trends from the past ten years indicates that while incidence rates have not significantly increased, the overall burden of the disease has grown due to improved survival rates and aging populations. From 1990 to 2019, the raw prevalence of schizophrenia increased from 14.2 million to 23.6 million, and disability-adjusted life years (DALYs) associated with the disease rose from 9.1 million to 15.1 million (Solmi et al., 2021; Global Burden of Disease Study, 2019).

Projection of these trends forward suggests a modest rise in the number of individuals living with schizophrenia. This is driven by factors such as better diagnosis and treatment options, leading to increased life expectancy among affected individuals. In countries with high socio-demographic index (SDI), both prevalence and DALYs have increased, indicating better detection and reporting but also highlighting the persistent burden of the disorder (Molecular Psychiatry, 2023).

Market for Treatment

The global market for schizophrenia treatment was valued at approximately $7.4 billion in 2022 and is projected to reach $12.6 billion by 2032, growing at a compound annual growth rate (CAGR) of 5.6% during the forecast period from 2023 to 2032. This market is anticipated to grow in the coming years due to several factors, including advancements in pharmacological therapies, increased awareness and diagnosis, and a greater emphasis on mental health. Novel treatment options, such as long-acting injectables and personalized medicine approaches, are expected to drive market expansion (Charlson et al., 2018; Global Burden of Disease Study, 2019).

Furthermore, the growing acceptance and destigmatization of mental health issues contribute to a larger market for schizophrenia treatments. Investment in research and development, along with government initiatives to improve mental health care infrastructure, also supports market growth. The U.S. market alone bears significant costs due to schizophrenia, with an estimated $281.6 billion spent in 2020 on medical care, lost productivity, and other related expenses (Psychiatrist.com, 2023).

Key Drugs for Schizophrenia with Highest Earning Potential

Several drugs currently dominate the market for schizophrenia treatment, each with substantial earning potential due to their widespread use, efficacy, and innovation in delivery methods.

1. Quetiapine (Seroquel)

- Quetiapine is one of the most prescribed antipsychotic medications, accounting for 27.5% of all antipsychotic prescriptions dispensed in the U.S. It is used extensively due to its effectiveness in treating both positive and negative symptoms of schizophrenia. The extended-release formulation, Seroquel XR, is particularly popular because it enhances patient compliance by reducing the frequency of dosing.

2. Aripiprazole (Abilify)

- Aripiprazole, marketed as Abilify, holds about 20.8% of the market share. It is known for its unique mechanism as a partial agonist at dopamine D2 receptors, which helps in balancing dopamine levels rather than just blocking them. This reduces the risk of certain side effects commonly associated with other antipsychotics. The recent approval of Abilify Asimtufii, a long-acting injectable administered once every two months, further enhances its market potential by addressing issues of medication adherence.

3. Risperidone (Risperdal)

- Risperidone is another key player, comprising 11.1% of the antipsychotic market. It is effective in treating a wide range of schizophrenia symptoms and is available in both oral and long-acting injectable forms. The injectable form, Risperdal Consta, is administered biweekly and is favored for its ability to ensure consistent therapeutic levels.

4. Olanzapine (Zyprexa)

- Olanzapine holds 9.6% of the market share. It is highly effective for acute and maintenance treatment of schizophrenia. Zyprexa Relprevv, its long-acting injectable formulation, provides a critical option for patients who struggle with daily medication adherence.

5. Cariprazine (Vraylar)

- Cariprazine is a newer entrant but has quickly gained a significant foothold with 4.2% market share. It is particularly noted for its efficacy in treating both schizophrenia and bipolar disorder, targeting dopamine D3 receptors, which might offer benefits in managing cognitive symptoms of schizophrenia.

Diagnostic Criteria

ICD-11 Code for Schizophrenia: 6A20

Diagnostic Criteria according to ICD-11:

1. Core Symptoms: The diagnosis of schizophrenia requires the presence of at least two of the following symptoms for a sizable portion of time during a period of at least one month (at least one qualifying symptom should be from the core symptoms):

- Delusions (disorganization in the form of thought)
- Hallucinations
- Disorganized thinking (typically inferred from disorganized speech)
- Experience of influence, passivity, or control

2. Exclusion of Other Conditions: The diagnosis should not be made if the disturbance is attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition. Additionally, the presence of schizotypal disorder, schizophrenic reaction and acute and transient psychotic disorder should be ruled out.

3. Additional symptoms: Negative symptoms such as alogia, paucity of speech, avolition, asociality and anhedonia. Psychomotor disturbances including catatonia, posturing, waxy flexibility, negativism, mutism, or stupor.

DSM-5 Code for Schizophrenia: 295.90 (F20.9)

Diagnostic Criteria According to DSM-5:

1. Core Symptoms: Like ICD-11, DSM-5 requires at least two of the following symptoms, each present for a significant portion of time during a one-month period. At least one of the symptoms must be delusions, hallucinations, or disorganized speech:

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (e.g., diminished emotional expression or avolition)

Evolution Over Time:

The diagnostic criteria for schizophrenia have undergone significant changes over the years, reflecting advancements in our understanding of the disorder. Earlier editions of the DSM, such as DSM-II and DSM-III, had broader and less specific criteria, which often led to inconsistent diagnoses. Over time, the criteria have been refined to improve reliability and validity, focusing on clearly defined symptoms and their impact on functioning.

Epidemiological Landscape of Schizophrenia

1. Genetic Predisposition

- **Heritability:** Schizophrenia has a strong genetic component, with heritability estimates around 80%. Individuals with a first-degree relative (parent, sibling) with schizophrenia have a 10% higher risk of developing the disorder compared to the general population.
- **Risk Genes:** Numerous genes have been implicated in schizophrenia, including those involved in dopamine regulation, neural development, and synaptic function.

2. Age

- **Typical Onset:** Schizophrenia typically manifests in late adolescence to early adulthood. The average age of onset is slightly earlier in males (18-25 years) compared to females (25-35 years).

3. Gender Differences

- **Prevalence:** While the overall prevalence of schizophrenia is similar between males and females, the course and presentation of the disorder can differ. Males often experience earlier onset and more severe negative symptoms, whereas females may have later onset and better overall prognosis.

4. Racial and Ethnic Differences

- **Diagnosis and Prevalence:** Schizophrenia affects all racial and ethnic groups; however, the prevalence and incidence rates can vary. For example, African Americans are more likely to be diagnosed with schizophrenia than white Americans.

5. Geographical Variations

- **Urban vs. Rural:** Higher prevalence rates of schizophrenia are reported in urban areas compared to rural areas. Factors contributing to this include increased exposure to environmental stressors, higher population density, and greater social adversity in urban settings.
- **Migration:** Migrant populations tend to have elevated rates of schizophrenia, potentially due to the stress of migration, socio-cultural integration challenges, and genetic-environmental interactions.

6. Environmental Influences

- **Prenatal Factors:** Prenatal exposure to infections, malnutrition, and stress can increase the risk of developing schizophrenia. Complications during birth, such as hypoxia, are also linked to a higher risk.
- **Childhood Adversities:** Trauma, abuse, and neglect during childhood are significant risk factors for schizophrenia. These adverse experiences can affect brain development and increase vulnerability to the disorder.
- **Substance Use:** Substance use, particularly cannabis use during adolescence, has been associated with an increased risk of schizophrenia. The exact relationship is complex, with cannabis potentially acting as a trigger in genetically predisposed individuals.

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Key Challenges in Determining Endpoints in Schizophrenia Clinical Trials

1. Symptom Reduction:

- **Subjective Reporting:** Symptom reduction, particularly for hallucinations and delusions, relies heavily on patient self-reporting, which can be influenced by various factors.
- **Variability in Symptoms:** The heterogeneity of schizophrenia symptoms makes it difficult to standardize measurements.

2. Quality of Life (QoL):

- **Multidimensional Nature:** Measuring it accurately requires comprehensive tools that can assess diverse domains.
- **Subjective Experience:** QoL is inherently subjective, with personal perceptions and expectations influencing assessments.

3. Time To Relapse:

- **Long Follow-Up Periods:** Relapse prevention requires long-term follow-up, which can be resource-intensive and difficult to maintain.
- **Defining Relapse:** Variations in the definition of relapse across studies can lead to inconsistent findings. Relapse can be defined by hospitalization, symptom exacerbation, or medication changes.

4. Functional Outcomes:

- Complex Measurement: Functional outcomes include various aspects such as employment, social relationships, and independent living skills, making comprehensive assessment challenging.

5. Cognitive Function:

- **Measurement Complexity:** Cognitive impairment can affect attention, memory, executive function, and social cognition. Measuring these domains requires specific and sensitive neuropsychological tests.
- **Variability:** Cognitive deficits vary widely among patients and can fluctuate over time.

6. Social Functioning:

- **Subjective and Objective Aspects:** Social functioning includes both subjective aspects (patient satisfaction with social relationships) and objective aspects (number of social interactions, quality of relationships), making it difficult to measure comprehensively.

7. Adherence to Treatment:

- **Self-Reported Data:** Treatment adherence is often measured through self-report, which can be unreliable due to recall bias or intentional misreporting.

8. Healthcare Utilization:

- **Data Collection:** Collecting comprehensive data on healthcare utilization, including hospitalizations, emergency room visits, and outpatient appointments, can be logistically challenging.

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Pivotal Endpoints for Schizophrenia Clinical Trials: Effective Solutions

1. Symptom Reduction:

Standardized Rating Scales: Utilizing validated tools like the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS) can help standardize symptom measurement across studies.

2. Quality of Life (QoL):

Patient-Reported Outcome Measures (PROMs): Incorporating PROMs such as the Schizophrenia Quality of Life Scale (SQLS) allows patients to provide direct input on their well-being.

3. Time To Relapse:

Clear Definitions: Establishing standardized criteria for defining relapse ensures consistency across studies.

Regular Monitoring: Implementing regular and systematic follow-up assessments helps detect early signs of relapse.

4. Functional Outcomes:

Multidisciplinary Approach: Collaborating with occupational therapists, social workers, and other professionals can offer a comprehensive assessment of functional capabilities and needs.

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5. Cognitive Function:

Standardized Testing Batteries: Using comprehensive and standardized cognitive testing batteries, such as the MATRICS Consensus Cognitive Battery (MCCB), can ensure consistent and reliable measurements.

6. Social Functioning:

Combination of Self-Report and Observer Ratings: Using both patient self-reports and clinician-rated scales, such as the Social Functioning Scale (SFS), can provide a more balanced assessment.

7. Adherence to Treatment:

Objective Measures: Using objective measures such as pill counts, pharmacy refill records, and electronic monitoring devices can provide more accurate adherence data.

8. Healthcare Utilization:

Electronic Health Records (EHR): Leveraging EHRs for data collection can provide accurate and detailed information on healthcare utilization.

Five FDA-Approved Treatments for Schizophrenia

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Clozapine	1989	Novartis	Dopamine D2 receptor antagonist with high affinity for serotonin 5-HT2A receptors	Effective in treatment-resistant schizophrenia, reduces suicidal behavior
Risperidone	1993	Janssen	Dopamine D2 and serotonin 5-HT2A receptor antagonist	Controls positive and negative symptoms, improves cognitive function
Olanzapine	1996	Eli Lilly	Dopamine and serotonin receptor antagonist	Reduces positive and negative symptoms, improves quality of life
Quetiapine	1997	AstraZeneca	Dopamine D2 and serotonin 5-HT2 receptor antagonist	Treats both positive and negative symptoms, used for acute and maintenance therapy
Aripiprazole	2002	Otsuka	Partial agonist at dopamine D2 and serotonin 5-HT1A receptors, antagonist at serotonin 5-HT2A receptors	Stabilizes mood, reduces positive symptoms, and has a lower risk of metabolic side effects

Approved Product Analysis: Clozapine

Treatment Resistant Schizophrenia

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Multicenter, randomized, double-blind, active-controlled study in treatment-resistant schizophrenia	Treatment response	BPRS, CGI-S	6 weeks	N=268 (CLOZARIL: 126, Chlorpromazine: 142)	• **Response Rate:** CLOZARIL: 30%, Chlorpromazine: 4%; statistically significant ($p < 0.001$) • **Change in BPRS Score:** CLOZARIL: -16, Chlorpromazine: -5; statistically significant ($p < 0.001$) • **Change in Key BPRS Item Scores:** CLOZARIL: -5, Chlorpromazine: -2; statistically significant ($p < 0.001$) • **Change in CGI-S Score:** CLOZARIL: -1.2, Chlorpromazine: -0.4; statistically significant ($p < 0.001$)

Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
International Suicide Prevention Trial (InterSePT™, a trademark of Novartis Pharmaceuticals Corporation) comparing CLOZARIL versus olanzapine	Time to significant suicide attempt, hospitalization due to imminent suicide risk, worsening of suicidality severity	CGI-SS-BP	104 weeks	N=956 (CLOZARIL: 478, Olanzapine: 478)	• **Probability of significant suicide attempt or hospitalization:** CLOZARIL: 24%, Olanzapine: 32%; 95% CI of the difference: 2%, 14% • **Delay in time to recurrent suicidal behavior:** Statistically significant longer delay for CLOZARIL ($p<0.001$) • **Worsening of suicidality severity:** Assessed by CGI-SS-BP, showing CLOZARIL as more effective in preventing worsening of suicidality severity

Approved Product Analysis: Risperidone

Schizophrenia

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult psychotic inpatients and outpatients with schizophrenia	12-week, placebo-controlled trial	Treatment response	PANSS total score	12 weeks	N=400	• **RISPERDAL® CONSTA® 25 mg:** Significant improvement in total PANSS score compared to placebo • **RISPERDAL® CONSTA® 50 mg:** Significant improvement in total PANSS score compared to placebo • **RISPERDAL® CONSTA® 75 mg:** Significant improvement in total PANSS score compared to placebo • **Placebo:** No significant improvement in total PANSS score • **Note:** No statistically significant differences between the three dose groups, but numerically less effect size for the 75 mg dose group compared to the 50 mg dose group

Bipolar Disorder – Monotheraphy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with Bipolar I Disorder	Multicenter, double-blind, placebo-controlled study	Time to relapse to any mood episode (depression, mania, hypomania, or mixed)	Not specified	26 weeks (open-label), variable duration (double-blind)	N=501 (open-label), N=303 (double-blind)	• **RISPERDAL® CONSTA®:** Delayed time to relapse compared to placebo • **Placebo:** Earlier relapse compared to RISPERDAL® CONSTA® • **Note:** Majority of relapses were due to manic symptoms

Bipolar Disorder – Adjunctive Therapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with Bipolar I Disorder (experiencing ≥4 episodes of mood disorder in the previous 12 months)	Multicenter, randomized, double-blind, placebo-controlled study	Time to relapse to any mood episode (depression, mania, hypomania, or mixed)	Not specified	16 weeks (open-label), 52 weeks (double-blind)	N=240 (open-label), N=124 (double-blind)	• **RISPERDAL® CONSTA® (25-50 mg) + mood stabilizer:** Delayed time to relapse compared to placebo • **Placebo + mood stabilizer:** Earlier relapse compared to RISPERDAL® CONSTA® • **Note:** Relapses were half depressive and half manic or mixed episodes

Approved Product Analysis: Olanzapine

Schizophrenia – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult inpatients with schizophrenia	6-week, placebo-controlled trial (1 mg/day and 10 mg/day olanzapine)	Treatment response	PANSS total, BPRS total, BPRS psychosis cluster, PANSS Negative subscale, CGI Severity	6 weeks	N=149	• **PANSS Total Score:** 10 mg/day superior to placebo • **BPRS Total Score:** 10 mg/day superior to placebo • **BPRS Psychosis Cluster:** 10 mg/day superior to placebo • **PANSS Negative Subscale:** 10 mg/day superior to placebo • **CGI Severity:** 10 mg/day superior to placebo
Adult inpatients with schizophrenia	6-week, placebo-controlled trial (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, 15 ± 2.5 mg/day olanzapine)	Treatment response	BPRS total, BPRS psychosis cluster, CGI Severity, SANS	6 weeks	N=253	• **BPRS Total Score:** 12 mg/day and 16 mg/day superior to placebo • **BPRS Psychosis Cluster:** 12 mg/day and 16 mg/day superior to placebo • **CGI Severity:** 12 mg/day and 16 mg/day superior to placebo • **SANS:** 16 mg/day superior to placebo; no clear advantage for 16 mg/day over 12 mg/day
Adult outpatients with schizophrenia	Longer-term trial (continuation on olanzapine vs. placebo)	Time to relapse	BPRS positive symptoms, hospitalization	Up to 12 months (stopped early at 8 months)	N=326	• **Time to Relapse:** Olanzapine superior to placebo in preventing relapse • **Relapse Definition:** Increase in BPRS positive symptoms or hospitalization; trial stopped early due to excess placebo relapses

Schizophrenia – Adolescents

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adolescents (13-17 years) with schizophrenia and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL)	6-week, double-blind, placebo-controlled, randomized trial	Treatment response	BPRS-C total score	6 weeks	N=107	• **BPRS-C Total Score:** Statistically significantly greater mean reduction for olanzapine (mean modal dose 12.5 mg/day, mean dose 11.1 mg/day) compared to placebo

Approved Product Analysis: Olanzapine (cont.)

Bipolar I Disorder (Manic or Mixed Episodes) – Adults – Monotherapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with bipolar I disorder (manic or mixed episodes)	3-week, placebo-controlled trial (5-20 mg/day, starting at 10 mg/day)	Treatment response	Y-MRS	3 weeks	N=67	• **Y-MRS Total Score:** Olanzapine superior to placebo in reduction of Y-MRS total score
Adults with bipolar I disorder (manic or mixed episodes)	3-week, placebo-controlled trial (identical design to first trial)	Treatment response	Y-MRS	3 weeks	N=67	• **Y-MRS Total Score:** Similar treatment difference to first trial, not superior to placebo due to sample size and site variability
Adults with bipolar I disorder (manic or mixed episodes)	4-week, placebo-controlled trial (5-20 mg/day, starting at 15 mg/day)	Treatment response	Y-MRS	4 weeks	N=115	• **Y-MRS Total Score:** Olanzapine superior to placebo in reduction of Y-MRS total score
Adults with bipolar I disorder (manic or mixed episodes)	Randomized trial following open-label phase (5-20 mg/day)	Time to relapse	Y-MRS, HAM-D 21	Observation period up to 59 days (olanzapine) and 23 days (placebo)	N=361 (olanzapine: 225, placebo: 136)	• **Time to Relapse:** Olanzapine superior to placebo in preventing relapse • **Discontinuation:** 50% of olanzapine group by day 59, 50% of placebo group by day 23

Bipolar I Disorder (Manic or Mixed Episodes) – Adults – Adjunct to Lithium or Valproate

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Dosage	Magnitude of Improvement
Adults with bipolar I disorder (manic or mixed episodes) on lithium or valproate	6-week, placebo-controlled combination trial	Treatment response	Y-MRS	6 weeks	N=175	Olanzapine: 5-20 mg/day, once daily (starting at 10 mg/day) Lithium: 0.6-1.2 mEq/L Valproate: 50-125 µg/mL	**Y-MRS Total Score:** Olanzapine combined with lithium or valproate superior to lithium or valproate alone in reduction of Y-MRS total score
Adults with bipolar I disorder (manic or mixed episodes) on lithium or valproate	6-week, placebo-controlled combination trial	Treatment response	Y-MRS	6 weeks	N=169	Olanzapine: 5-20 mg/day, once daily (starting at 10 mg/day) Lithium: 0.6-1.2 mEq/L Valproate: 50-125 µg/mL	**Y-MRS Total Score:** Olanzapine combined with lithium or valproate superior to lithium or valproate alone in reduction of Y-MRS total score

Approved Product Analysis: Olanzapine (cont.)

Bipolar I Disorder (Manic or Mixed Episodes) – Adolescents – Acute Monotherapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adolescents with bipolar I disorder (ages 13-17 years) and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL)	3-week, double-blind, placebo-controlled, randomized trial	Reduction in manic or mixed episode symptoms	Adolescent Structured Young-Mania Rating Scale (Y-MRS), DSM-IV-TR, K-SADS-PL	3 weeks	N=161	• **Y-MRS Total Score:** Olanzapine (2.5 to 20 mg/day) was more effective than placebo with a statistically significantly greater mean reduction in Y-MRS total score. • **Mean Modal Dose:** 10.7 mg/day • **Mean Dose:** 8.9 mg/day

Agitation Associated with Schizophrenia and Bipolar I Mania

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Agitated adult inpatients with schizophrenia	Placebo-controlled trial	Treatment response	PANSS Excited Component	2 hours post-injection	N=270	• **PANSS Excited Component:** All doses (2.5 mg, 5 mg, 7.5 mg, 10 mg) statistically superior to placebo; larger and more consistent effect for 5 mg, 7.5 mg, and 10 mg; no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose
Agitated adult inpatients with schizophrenia	Placebo-controlled trial	Treatment response	PANSS Excited Component	2 hours post-injection	N=311	• **PANSS Excited Component:** 10 mg olanzapine statistically superior to placebo
Agitated adult inpatients with bipolar I disorder (manic or mixed episodes)	Placebo-controlled trial	Treatment response	PANSS Excited Component	2 hours post-injection	N=201	• **PANSS Excited Component:** 10 mg olanzapine statistically superior to placebo

Approved Product Analysis: Quetiapine

Schizophrenia – Short-term Trials – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with schiz-ophrenia	Study 1: 6-week, fixed-dose, placebo-controlled trial	Treatment response	PANSS total score	6 weeks	N=573	• **SEROQUEL XR 400 mg/day:** Mean change from baseline: -24.8 (2.5), statistically significant vs. placebo (-6.1, CI: -11.5 to -0.6) • **SEROQUEL XR 600 mg/day:** Mean change from baseline: -30.9 (2.5), statistically significant vs. placebo (-12.1, CI: -17.6 to -6.7) • **SEROQUEL XR 800 mg/day:** Mean change from baseline: -31.3 (2.5), statistically significant vs. placebo (-12.5, CI: -17.9 to -7.1) • **SEROQUEL 400 mg/day (twice daily):** Mean change from baseline: -26.6 (2.4), statistically significant vs. placebo (-7.8, CI: -13.1 to -2.4) • **Placebo:** Mean change from baseline: -18.8 (2.5)

Schizophrenia – Short Term Trials – Adolescents (ages 13-17)

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adolescents (13-17 years) with schizophrenia	Study 2: 6-week, double-blind, placebo-controlled trial	Treatment response	PANSS total score	6 weeks	N=222 (SEROQUEL 400 mg/day: 73, SEROQUEL 800 mg/day: 74, Placebo: 75)	• **SEROQUEL 400 mg/day:** Mean change from baseline: -27.3 (2.6), statistically significant vs. placebo (-8.2, CI: -16.1 to -0.3) • **SEROQUEL 800 mg/day:** Mean change from baseline: -28.4 (1.8), statistically significant vs. placebo (-9.3, CI: -16.2 to -2.4) • **Placebo:** Mean change from baseline: -19.2 (3.0)

Schizophrenia – Maintenance Trials

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Clinically stable adult outpatients with schizophrenia	Study 3: Longer-term, double-blind, placebo-controlled trial	Time to relapse	PANSS total score, CGI-S, CGI-I	Up to 7 months	N=171	• **Time to Relapse:** SEROQUEL XR (400-800 mg/day) statistically significant longer time to relapse compared to placebo • **Relapse Criteria:** ≥30% increase in PANSS total score, CGI-I score of ≥6, hospitalization due to worsening of schizophrenia, or need for any other antipsychotic medication

Approved Product Analysis: Quetiapine (cont.)

Bipolar I disorder, manic or mixed episodes – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar I disorder (manic or mixed episodes)	Study 1: 3-week, placebo-controlled trial	Treatment response	YMRS total score	3 weeks	N=316	• **SEROQUEL XR (400-800 mg/day):** Mean change from baseline: -14.3 (0.9), statistically significant vs. placebo (-3.8, CI: -5.7 to -2.0) • **Placebo:** Mean change from baseline: -10.5 (0.9)

Monotherapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar I disorder (manic episodes)	Study 2: 12-week, placebo-controlled trial	Treatment response	YMRS total score	12 weeks	N=300	• **SEROQUEL (200-800 mg/day):** Mean change from baseline: -12.3 (1.3), statistically significant vs. placebo (-4.0, CI: -7.0 to -1.0) • **Haloperidol:** Mean change from baseline: -15.7 (1.3), statistically significant vs. placebo (-7.4, CI: -10.4 to -4.4) • **Placebo:** Mean change from baseline: -8.3 (1.3)
Patients with bipolar I disorder (manic episodes)	Study 3: 12-week, placebo-controlled trial	Treatment response	YMRS total score	12 weeks	N=299	• **SEROQUEL (200-800 mg/day):** Mean change from baseline: -14.6 (1.5), statistically significant vs. placebo (-7.9, CI: -10.9 to -5.0) • **Lithium:** Mean change from baseline: -15.2 (1.6), statistically significant vs. placebo (-8.5, CI: -11.5 to -5.5) • **Placebo + mood stabilizer:** Mean change from baseline: -6.7 (1.6)

Bipolar I disorder, manic or mixed episodes – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar I disorder (manic or mixed episodes)	Study 1: 3-week, placebo-controlled trial	Treatment response	YMRS total score	3 weeks	N=316	• **SEROQUEL XR (400-800 mg/day):** Mean change from baseline: -14.3 (0.9), statistically significant vs. placebo (-3.8, CI: -5.7 to -2.0) • **Placebo:** Mean change from baseline: -10.5 (0.9)

Approved Product Analysis: Quetiapine (cont.)

Monotherapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar I disorder (manic episodes)	Study 2: 12-week, placebo-controlled trial	Treatment response	YMRS total score	12 weeks	N=300	• **SEROQUEL (200-800 mg/day):** Mean change from baseline: -12.3 (1.3), statistically significant vs. placebo (-4.0, CI: -7.0 to -1.0) • **Haloperidol:** Mean change from baseline: -15.7 (1.3), statistically significant vs. placebo (-7.4, CI: -10.4 to -4.4) • **Placebo:** Mean change from baseline: -8.3 (1.3)
Patients with bipolar I disorder (manic episodes)	Study 3: 12-week, placebo-controlled trial	Treatment response	YMRS total score	12 weeks	N=299	• **SEROQUEL (200-800 mg/day):** Mean change from baseline: -14.6 (1.5), statistically significant vs. placebo (-7.9, CI: -10.9 to -5.0) • **Lithium:** Mean change from baseline: -15.2 (1.6), statistically significant vs. placebo (-8.5, CI: -11.5 to -5.5) • **Placebo + mood stabilizer:** Mean change from baseline: -6.7 (1.6)

Adjunct Therapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar mania (adjunct to lithium or divalproex)	Study 4: 3-week, placebo-controlled trial	Treatment response	YMRS total score	3 weeks	N=170	• **SEROQUEL (200-800 mg/day) + mood stabilizer:** Mean change from baseline: -13.8 (1.6), statistically significant vs. placebo (-3.8, CI: -7.1 to -0.6) • **Placebo + mood stabilizer:** Mean change from baseline: -10 (1.5)

Children and Adolescents (ages 10-17)

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Children and adolescents (10-17 years) with bipolar I disorder (manic episodes)	3-week, double-blind, placebo-controlled, multicenter trial	Treatment response	YMRS total score	3 weeks	N=284 (SEROQUEL 400 mg/day: 95, SEROQUEL 600 mg/day: 98, Placebo: 91)	• **SEROQUEL 400 mg/day:** Mean change from baseline: -14.3 (0.96), statistically significant vs. placebo (-5.2, CI: -8.1 to -2.3) • **SEROQUEL 600 mg/day:** Mean change from baseline: -15.6 (0.97), statistically significant vs. placebo (-6.6, CI: -9.5 to -3.7) • **Placebo:** Mean change from baseline: -9.0 (1.1)

Approved Product Analysis: Quetiapine (cont.)

Bipolar Disorder, Depressive Episodes – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar disorder (depressive episodes)	Study 6: 8-week, randomized, double-blind, placebo-controlled	Treatment response	MADRS total score	8 weeks	N=280	• **SEROQUEL XR 300 mg/day:** Mean change from baseline: -17.4 (1.2), statistically significant vs. placebo (-5.5, CI: -7.9 to -3.2) • **Placebo:** Mean change from baseline: -11.9 (1.2)
Patients with bipolar disorder (depressive episodes)	Study 7: 8-week, randomized, double-blind, placebo-controlled	Treatment response	MADRS total score, Q-LES-Q(SF)	8 weeks	N=522	• **SEROQUEL 300 mg/day:** Mean change from baseline: -16.4 (0.9), statistically significant vs. placebo (-6.1, CI: -8.3 to -3.9) • **SEROQUEL 600 mg/day:** Mean change from baseline: -16.7 (0.9), statistically significant vs. placebo (-6.5, CI: -8.7 to -4.3) • **Placebo:** Mean change from baseline: -10.3 (0.9) • **Quality of Life (Q-LES-Q(SF)):** Statistically significant improvements over placebo for 300 mg dose group • *No additional benefit was seen with the 600 mg dose*
Patients with bipolar disorder (depressive episodes)	Study 8: 8-week, randomized, double-blind, placebo-controlled	Treatment response	MADRS total score, Q-LES-Q(SF)	8 weeks	N=523	• **SEROQUEL 300 mg/day:** Mean change from baseline: -16.9 (1.0), statistically significant vs. placebo (-5.0, CI: -7.3 to -2.7) • **SEROQUEL 600 mg/day:** Mean change from baseline: -16.0 (1.0), statistically significant vs. placebo (-4.1, CI: -6.4 to -1.8) • **Placebo:** Mean change from baseline: -11.9 (1.0) • **Quality of Life (Q-LES-Q(SF)):** Statistically significant improvements over placebo for 300 mg dose group • *No additional benefit was seen with the 600 mg dose*

Approved Product Analysis: Quetiapine (cont.)

Maintenance Treatment as an Adjunct to Lithium or Divalproex

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with bipolar I disorder (maintenance treatment)	Study 9: Placebo-controlled trial	Time to recurrence of a mood event (manic, mixed, or depressed episode)	YMRS, MADRS, Kaplan-Meier	280 days (SEROQUEL) and 117 days (placebo)	N=1326	• **Time to Recurrence:** SEROQUEL superior to placebo in increasing time to recurrence of any mood event. • **Discontinuation:** 50% of SEROQUEL group discontinued by day 280, 50% of placebo group discontinued by day 117
Patients with bipolar I disorder (maintenance treatment)	Study 10: Placebo-controlled trial	Time to recurrence of a mood event (manic, mixed, or depressed episode)	YMRS, MADRS, Kaplan-Meier	280 days (SEROQUEL) and 117 days (placebo)	N=1326	• **Time to Recurrence:** SEROQUEL superior to placebo in increasing time to recurrence of any mood event. • **Discontinuation:** 50% of SEROQUEL group discontinued by day 280, 50% of placebo group discontinued by day 117

Approved Product Analysis: Aripiprazole

Schizophrenia – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Acutely relapsed inpatients with schizophrenia	Study 1: 4-week, placebo-controlled trial	Treatment response	PANSS total score, PANSS positive subscale, PANSS negative subscale, CGI-severity score	4 weeks	N=414	• **ABILIFY 15 mg/day:** Mean change from baseline: -15.5 (2.40), statistically significant vs. placebo (-12.6, CI: -18.9 to -6.2) • **ABILIFY 30 mg/day:** Mean change from baseline: -11.4 (2.39), statistically significant vs. placebo (-8.5, CI: -14.8 to -2.1) • **Placebo:** Mean change from baseline: -2.9 (2.36)
Acutely relapsed inpatients with schizophrenia	Study 2: 4-week, placebo-controlled trial	Treatment response	PANSS total score, PANSS positive subscale, PANSS negative subscale, CGI-severity score	4 weeks	N=404	• **ABILIFY 20 mg/day:** Mean change from baseline: -14.5 (2.23), statistically significant vs. placebo (-9.6, CI: -15.4 to -3.8) • **ABILIFY 30 mg/day:** Mean change from baseline: -13.9 (2.24), statistically significant vs. placebo (-9.0, CI: -14.8 to -3.1) • **Placebo:** Mean change from baseline: -5.0 (2.17)
Acutely relapsed inpatients with schizophrenia	Study 3: 6-week, placebo-controlled trial	Treatment response	PANSS total score, PANSS positive subscale, PANSS negative subscale	6 weeks	N=420	• **ABILIFY 10 mg/day:** Mean change from baseline: -15.0 (2.38), statistically significant vs. placebo (-12.7, CI: -19.0 to -6.4) • **ABILIFY 15 mg/day:** Mean change from baseline: -11.7 (2.38), statistically significant vs. placebo (-9.4, CI: -15.7 to -3.1) • **ABILIFY 20 mg/day:** Mean change from baseline: -14.4 (2.45), statistically significant vs. placebo (-12.1, CI: -18.5 to -5.7) • **Placebo:** Mean change from baseline: -2.3 (2.35)
Acutely relapsed inpatients with schizophrenia	Study 4: 6-week, placebo-controlled trial	Treatment response	PANSS total score	6 weeks	N=367	• **ABILIFY 2 mg/day:** Mean change from baseline: -8.2 (1.90), not statistically significant vs. placebo (-2.9, CI: -8.3 to 2.5) • **ABILIFY 5 mg/day:** Mean change from baseline: -10.6 (1.93), not statistically significant vs. placebo (-5.2, CI: -10.7 to 0.2) • **ABILIFY 10 mg/day:** Mean change from baseline: -11.3 (1.88), statistically significant vs. placebo (-5.9, CI: -11.3 to -0.6) • **Placebo:** Mean change from baseline: -5.3 (1.97)
Symptomatically stable inpatients or outpatients with schizophrenia	Study 5: 26-week, placebo-controlled trial	Time to relapse	CGI-Improvement, PANSS total score	26 weeks	N=310	• **ABILIFY 15 mg/day:** Statistically significant longer time to relapse compared to placebo

Approved Product Analysis: Aripiprazole (cont.)

Schizophrenia – Pediatric Patients

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (13-17 years) with schizophrenia	Study 6: 6-week, placebo-controlled trial	Treatment response	PANSS total score	6 weeks	N=302	• **ABILIFY 10 mg/day:** Mean change from baseline: -26.7 (1.91), statistically significant vs. placebo (-5.5, CI: -10.7 to -0.2) • **ABILIFY 30 mg/day:** Mean change from baseline: -28.6 (1.92), statistically significant vs. placebo (-7.4, CI: -12.7 to -2.1) • **Placebo:** Mean change from baseline: -21.2 (1.93)

Bipolar Disorder

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Hospitalized patients with bipolar I disorder (manic or mixed episodes)	Study 1: 3-week, placebo-controlled trial	Treatment response	Y-MRS total score, CGI-BP Severity of Illness (mania)	3 weeks	N=268	- **ABILIFY 30/15 mg/day:** Mean change from baseline: -12.52 (1.05), statistically significant vs. placebo (-5.33, CI: -7.90 to -2.76) - **Placebo:** Mean change from baseline: -7.19 (1.07)
Hospitalized patients with bipolar I disorder (manic or mixed episodes)	Study 2: 3-week, placebo-controlled trial	Treatment response	Y-MRS total score, CGI-BP Severity of Illness (mania)	3 weeks	N=248	- **ABILIFY 30/15 mg/day:** Mean change from baseline: -8.15 (1.23), statistically significant vs. placebo (-4.80, CI: -7.80 to -1.80) - **Placebo:** Mean change from baseline: -3.35 (1.22)
Hospitalized patients with bipolar I disorder (manic or mixed episodes)	Study 3: 3-week, placebo-controlled trial	Treatment response	Y-MRS total score, CGI-BP Severity of Illness (mania)	3 weeks	N=480	- **ABILIFY 15-30 mg/day:** Mean change from baseline: -12.64 (0.84), statistically significant vs. placebo (-3.63, CI: -5.75 to -1.51) - **Placebo:** Mean change from baseline: -9.01 (0.81)
Hospitalized patients with bipolar I disorder (manic or mixed episodes)	Study 4: 3-week, placebo-controlled trial	Treatment response	Y-MRS total score, CGI-BP Severity of Illness (mania)	3 weeks	N=485	- **ABILIFY 15-30 mg/day:** Mean change from baseline: -11.98 (0.80), statistically significant vs. placebo (-2.28, CI: -4.44 to -0.11) - **Placebo:** Mean change from baseline: -9.70 (0.83)

Approved Product Analysis: Aripiprazole (cont.)

Bipolar Disorder – Adjunctive Therapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with bipolar I disorder (manic or mixed episodes)	Study 5: 6-week, placebo-controlled trial	Treatment response	Y-MRS total score, CGI-BP Severity of Illness (mania)	6 weeks	N=384	• **ABILIFY (15 or 30 mg/day) + Lithium/Valproate:** Mean change from baseline: -13.31 (0.50), statistically significant vs. placebo (-2.62, CI: -4.29 to -0.95) • **Placebo + Lithium/Valproate:** Mean change from baseline: -10.70 (0.69)

Bipolar Disorder – Pediatric Patients

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (10-17 years) with bipolar I disorder (manic or mixed episodes)	Study 6: 4-week, placebo-controlled trial	Treatment response	Y-MRS total score	4 weeks	N=296	• **ABILIFY 10 mg/day:** Mean change from baseline: -14.2 (0.89), statistically significant vs. placebo (-5.99, CI: -8.49 to -3.50) • **ABILIFY 30 mg/day:** Mean change from baseline: -16.5 (0.87), statistically significant vs. placebo (-8.26, CI: -10.7 to -5.77) • **Placebo:** Mean change from baseline: -8.2 (0.91)

Bipolar I Disorder – Monotherapy Maintenance Therapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with bipolar I disorder (recent manic or mixed episode)	Study 7: Maintenance trial	Time to relapse	Kaplan-Meier Estimation	182 days (approximately 6 months)	N=161	• **ABILIFY 15 or 30 mg/day:** Superior to placebo in time to relapse • **Relapse Rates:** 19 mood events in ABILIFY group vs. 36 in placebo group • **Manic Episodes:** 6 in ABILIFY group vs. 19 in placebo group • **Depressive Episodes:** 9 in ABILIFY group vs. 11 in placebo group

Approved Product Analysis: Aripiprazole (cont.)

Bipolar I Disorder – Adjunctive Maintenance Therapy

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with bipolar I disorder (recent manic or mixed episode)	Study 8: Adjunctive maintenance trial	Time to relapse to any mood event	Y-MRS, MADRS, Kaplan-Meier Estimation	52 weeks	N=337	• **ABILIFY + Lithium/Valproate:** Superior to placebo in time to relapse, as shown by Kaplan-Meier curves • **Relapse Rates:** 25 mood events in ABILIFY group vs. 43 in placebo group • **Manic Episodes:** 7 in ABILIFY group vs. 19 in placebo group • **Depressive Episodes:** 14 in ABILIFY group vs. 18 in placebo group

Adjunctive Treatment of Major Depressive Disorder – Adults

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adult patients with MDD and inadequate response to prior antidepressant therapy	Study 1: 6-week, placebo-controlled trial	Treatment response	MADRS total score, HAMD17, CGI-I, SDS	6 weeks	N=381	• **ABILIFY (5-20 mg/day) + Antidepressant:** Mean change from baseline: -8.49 (0.66), statistically significant vs. placebo (-2.84, CI: -4.53 to -1.15) • **Placebo + Antidepressant:** Mean change from baseline: -5.65 (0.64)
Adult patients with MDD and inadequate response to prior antidepressant therapy	Study 2: 6-week, placebo-controlled trial	Treatment response	MADRS total score, HAMD17, CGI-I, SDS	6 weeks	N=362	• **ABILIFY (5-20 mg/day) + Antidepressant:** Mean change from baseline: -8.78 (0.63), statistically significant vs. placebo (-3.01, CI: -4.66 to -1.37) • **Placebo + Antidepressant:** Mean change from baseline: -5.77 (0.67)

Approved Product Analysis: Aripiprazole (cont.)

Irritability Associated with Autistic Disorder – Pediatric Patients

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (6-17 years) with autistic disorder meeting DSM-IV criteria	Study 1: 8-week, placebo-controlled trial	Treatment response	ABC-I, CGI-I	8 weeks	N=98	• **ABILIFY (2-15 mg/day):** Mean change from baseline: -12.9 (1.44), statistically significant vs. placebo (-7.9, CI: -11.7 to -4.1) • **Placebo:** Mean change from baseline: -5.0 (1.43)
Pediatric patients (6-17 years) with autistic disorder meeting DSM-IV criteria	Study 2: 8-week, placebo-controlled trial	Treatment response	ABC-I, CGI-I	8 weeks	N=218	• **ABILIFY 5 mg/day:** Mean change from baseline: -12.4 (1.36), statistically significant vs. placebo (-4.0, CI: -7.7 to -0.4) • **ABILIFY 10 mg/day:** Mean change from baseline: -13.2 (1.25), statistically significant vs. placebo (-4.8, CI: -8.4 to -1.3) • **ABILIFY 15 mg/day:** Mean change from baseline: -14.4 (1.31), statistically significant vs. placebo (-6.0, CI: -9.6 to -2.3) • **Placebo:** Mean change from baseline: -8.4 (1.39)

Tourette's Disorder – Pediatric Patients

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients (7-17 years) with Tourette's disorder meeting DSM-IV criteria	Study 1: 8-week, placebo-controlled trial	Treatment response	YGTSS TTS, CGI-TS	8 weeks	N=133	• **ABILIFY (low dose):** Mean change from baseline: -13.4 (1.59), statistically significant vs. placebo (-6.3, CI: -10.2 to -2.3) • **ABILIFY (high dose):** Mean change from baseline: -16.9 (1.61), statistically significant vs. placebo (-9.9, CI: -13.8 to -5.9) • **Placebo:** Mean change from baseline: -7.1 (1.55)
Pediatric patients (6-18 years) with Tourette's disorder meeting DSM-IV criteria	Study 2: 10-week, placebo-controlled, flexible-dose trial	Treatment response	YGTSS TTS, CGI-TS	10 weeks	N=61	• **ABILIFY (2-20 mg/day):** Mean change from baseline: -15.0 (1.51), statistically significant vs. placebo (-5.3, CI: -9.8 to -0.9) • **Placebo:** Mean change from baseline: -9.6 (1.64)

Approved Product Analysis: Aripiprazole (cont.)

Agitation Associated with Schizophrenia or Bipolar Mania

Population	Study	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Agitated inpatients meeting DSM-IV criteria for schizophrenia	Study 1: 24-hour, placebo-controlled trial	Treatment response	PANSS Excited Component, CGI-I	2 hours post-injection	N=350	• **ABILIFY (1 mg):** Mean change from baseline: -4.47 (0.72), not statistically significant vs. placebo (-1.19, CI: -2.96 to 0.59) • **ABILIFY (5.25 mg):** Mean change from baseline: -5.65 (0.68), statistically significant vs. placebo (-2.37, CI: -4.10 to -0.63) • **ABILIFY (9.75 mg):** Mean change from baseline: -6.80 (0.72), statistically significant vs. placebo (-3.04, CI: -5.18 to -1.62) • **ABILIFY (15 mg):** Mean change from baseline: -6.87 (0.72), statistically significant vs. placebo (-2.44, CI: -4.21 to -0.66) • **Placebo:** Mean change from baseline: -3.28 (0.72)
Agitated inpatients meeting DSM-IV criteria for schizophrenia	Study 2: 24-hour, placebo-controlled trial	Treatment response	PANSS Excited Component, CGI-I	2 hours post-injection	N=445	• **ABILIFY (9.75 mg):** Mean change from baseline: -7.27 (0.59), statistically significant vs. placebo (-2.48, CI: -3.77 to -1.19) • **Placebo:** Mean change from baseline: -4.78 (0.69)
Agitated inpatients meeting DSM-IV criteria for bipolar I disorder (manic or mixed)	Study 3: 24-hour, placebo-controlled trial	Treatment response	PANSS Excited Component, CGI-I	2 hours post-injection	N=291	• **ABILIFY (9.75 mg):** Mean change from baseline: -8.74 (0.57), statistically significant vs. placebo (-2.99, CI: -4.53 to -1.44) • **ABILIFY (15 mg):** Mean change from baseline: -8.67 (0.57), statistically significant vs. placebo (-2.91, CI: -4.44 to -1.38) • **Placebo:** Mean change from baseline: -5.76 (0.58)

Summary of Failed Drug Candidates for Schizophrenia

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure
N-acetylcysteine	GDCT0251520	• Trial was terminated due to COVID-19-unable to continue recruitment and funding issues. • Based on findings, neither negative symptoms nor cognitive symptoms were significantly improved by 52 weeks treatment of two grams of n-acetyl cysteine daily for treatment resistance clozapine subjects.
Mirtazapine ODT	GDCT0096775	• Findings suggest that mirtazapine adjunctive to atypical antipsychotic treatment is not effective in treating the schizophrenic subjects.
Paliperidone ER	NCT00524043	• Paliperidone ER 1.5 mg although did not show any efficacy, was tolerable with a safety profile comparable to placebo in subjects with acute schizophrenia.
Tocilizumab	NCT02034474	• There were no observed treatment effects.
Citalopram	NCT01032083	• Adjunctive citalopram did not improve overall negative symptoms, quality of life and no serious safety or tolerability events were reported.

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Common Failure Points in Clinical Trials for Schizophrenia

1. High Placebo Rates:

Schizophrenia trials often exhibit high placebo response rates. Patients in the placebo group can show significant improvements due to therapeutic environment, patient expectations, and the natural course of the disease.

Impact: High placebo response rates can obscure the true efficacy of the investigational drug.

2. Symptom Heterogeneity:

Schizophrenia is characterized by a wide range of symptoms, including positive symptoms, negative symptoms, and cognitive deficits. This heterogeneity makes it challenging to design trials that can capture the full spectrum of the disorder.

Impact: Trials may fail to demonstrate efficacy if the treatment only addresses a subset of symptoms.

3. Diagnostic Inconsistencies:

Variability in diagnostic criteria and the subjective nature of symptom assessment can lead to inconsistencies in patient selection. Different diagnostic tools and inter-rater variability can result in a heterogeneous trial population.

Impact: Inconsistent criteria can lead to variability in baseline characteristics, affecting reliability of trial outcomes.

4. Poor Medication Adherence:

Patients with schizophrenia often struggle with medication adherence due to cognitive deficits, and the side effects of antipsychotic medications. Poor adherence can lead to fluctuations in symptom severity and confound trial outcomes.

Impact: Non-adherence can result in underestimation of a drug's efficacy and an overestimation of its side effects.

5. Cognitive Impairment:

Cognitive deficits are a core feature of schizophrenia but are often inadequately addressed in clinical trials. Cognitive impairment can affect patients' ability to participate in and comply with procedures.

Impact: High dropout rates and incomplete data can reduce the statistical power of the study and compromise the validity of the findings.

6. Social and Functional Impairment:

Schizophrenia significantly impacts social and functional abilities, which can influence trial outcomes. Patients may have difficulty maintaining regular follow-up appointments and engaging in study-related activities.

Impact: Irregular follow-up and poor engagement can lead to missing data and reduce the overall trial quality.

Safety Concerns and Standard of Care Treatment Options

Safety Concerns

1. Metabolic Side Effects:

- Many antipsychotic medications are associated with **significant weight gain**, increasing risk of cardiovascular disease, diabetes, etc.
- These medications can also cause insulin resistance and lipid abnormalities, contributing to type 2 **diabetes and dyslipidemia**.

2. Cardiovascular Risks:

- Some antipsychotic drugs can **prolong the QT interval** on an electrocardiogram (ECG), which increases the risk of arrhythmias.
- Antipsychotics can cause blood pressure changes, including **hypertension, hypotension, and orthostatic hypotension**.

3. Neurological Side Effects:

- **Extrapyramidal Symptoms (EPS)** include tremors, rigidity, bradykinesia, and tardive dyskinesia (involuntary movements).
- Many antipsychotics cause **sedation**, which can impair function.

4. Agranulocytosis and Blood Dyscrasias:

- Clozapine carries a significant risk of **agranulocytosis**, a severe reduction in white blood cells that increases the risk of infection.

5. Prolactin Elevation:

- Drugs like Risperidone and Paliperidone can elevate prolactin levels, leading to side effects such as galactorrhea, gynecomastia, menstrual disturbances, and sexual dysfunction.

Standard of Care Treatment Options

1. Pharmacological Treatments:

- **First-Generation Antipsychotics (FGAs):** These primarily act by blocking dopamine D2 receptors. While effective in reducing positive symptoms, they are often associated with higher rates of EPS.
- **Second-Generation Antipsychotics (SGAs):** SGAs are preferred due to their lower risk of EPS and broader efficacy in treating both positive and negative symptoms.

2. Psychosocial Interventions:

- **Cognitive Behavioral Therapy (CBT):** CBT helps patients manage symptoms by changing patterns of thinking and behavior. It is effective in reducing the severity of psychotic symptoms and improving functional outcomes.
- **Social Skills Training:** This intervention helps patients integrate better into society and maintain relationships.

3. Supportive Services:

- **Case Management:** Case managers coordinate care, connect patients with services, and provide support in navigating the healthcare system.

4. Early Intervention Services:

- **First-Episode Psychosis Programs:** These programs provide comprehensive care, including medication management, psychotherapy, and family support.

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Enhancing Clinical Trial Protocols for Schizophrenia

Improving clinical trial protocols is pivotal to advancing our understanding and treatment of Schizophrenia. The goal is not only to discover new therapeutic strategies but also to ensure these interventions meet the high safety and efficacy standards required for FDA approval.

1. Regulatory Insights:

- **Early and Continuous Engagement with the FDA**
  - Initiate discussions with the FDA during the pre-Investigational New Drug (IND) application phase.
  - Maintain regular contact with the FDA to ensure that the study remains compliant with evolving guidelines.
- **Incorporating Patient-Centered Outcomes**
  - Engage patients and caregivers to identify meaningful outcomes that reflect real-world benefits (PFDD).
  - Utilize Patient-Reported Outcome Measures to capture the patient's perspective on treatment efficacy and QoL.

2. Addressing Common Trial Challenges:

- **Mitigating Placebo Response**
  - Use techniques such as active placebos, extended lead-in periods, and centralized rating to reduce placebo response rates. Ensuring that patients and raters are appropriately blinded can also minimize bias.
- **Improving Patient Recruitment and Retention**
  - Recruit a diverse patient population that reflects real-world demographics, enhancing the generalizability of the findings.
  - Provide comprehensive patient support services.

2. Leveraging Technology and Innovation:

- **Digital Health Tools**
  - Use Electronic Health Records for efficient data collection and patient monitoring.
  - Implement mobile health applications for real-time symptom tracking, medication reminders, and patient-reported outcomes.
- **Artificial Intelligence (AI) and Machine Learning**
  - Machine learning algorithms analyze large datasets to uncover patterns that inform trial design and patient stratification.
  - AI can automate data analysis, reducing time and cost.

4. Ensuring Data Quality and Integrity:

- **Centralized Data Monitoring**
  - Implement centralized monitoring to ensure data consistency and accuracy across study sites.
- **Compliance with Good Clinical Practice (GCP)**
  - Ensure that all study personnel are trained in GCP guidelines. Regular training sessions and updates can help maintain high standards of conduct and data quality.
  - Conduct regular internal audits and prepare for external inspections to ensure compliance with regulatory requirements.

Notable Key Opinion Leaders in Schizophrenia Research

Name	Specialty	Designation	Location	Brief Bio
Dr. Leonard (Leo) Chen, MBBS MPsych FRANZCP AFRACMA	Psychiatry	Director, Alfred Health Victoria	Victoria, Australia	Dr. Leonard (Leo) Chen is the Director of Psychiatry Training at Alfred Health and also serves as the Head of the Psychopharmacology Research Team at the Monash Alfred Psychiatry Research Centre (MAPrc). He is involved in both clinical practice and research at Alfred Health and Epworth Healthcare. His work is heavily focused on improving the efficacy of treatments for depressive disorders through research on Transcranial Magnetic Stimulation (TMS) and the therapeutic potential of novel pharmacological agents.
Dr. Sonia Sharma Ghai, MBBS, DPM, DNB, FRANZCP	Psychiatry	Consultant Psychiatrist, Ballarat Psychiatry Group	Victoria, Australia	Dr. Sonia Sharma Ghai is a consultant general adult psychiatrist at the Ballarat Psychiatry Group in Ballarat, Victoria. Dr. Ghai is committed to providing quality, evidence-based treatment through detailed assessments and a holistic approach, combining psychotherapy and medications. She specializes in treating a range of psychiatric disorders, including depression, anxiety, OCD, PTSD, psychosis, and bipolar disorder. Additionally, she has a special interest in perinatal psychiatry, women's mental health, and co-morbid medical and psychiatric disorders.
Dr. Harish Kalra MBBS, FRANZCP	Psychiatry	Consultant Psychiatrist, Ballarat Psychiatry Group	Victoria, Australia	Dr. Harish Kalra is a well-respected psychiatrist based in Ballarat with over 24 years of experience in the field. He currently practices at the Mair Street Clinic in Ballarat. He is known for providing a compassionate and comprehensive approach to mental health care, utilizing therapeutic approaches such as Cognitive Behavioral Therapy (CBT) and Interpersonal Therapy (IPT). Dr. Kalra's clinical interests also include treating conditions like depression, bipolar disorder, schizophrenia, and post-traumatic stress disorders.
Dr. Rajul Tandon, MBBS, FRANZCP	Psychiatry	Consultant Psychiatrist, Ballarat Psychiatry Group	Victoria, Australia	Dr. Rajul Tandon is a consultant general adult psychiatrist at the Ballarat Psychiatry Group in Ballarat, Victoria. Dr. Tandon specializes in treating a wide range of psychiatric conditions, including depression, bipolar disorder, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), brief psychosis, schizophrenia, delusional disorder, and personality disorders. He has a strong interest in psychiatric research and has been involved in various service improvement activities.
Dr. Ramon Mocellin, MBBS, MSc, Master of Psychiatry, FRANZCO	Psychiatry and Neurology	Neuropsychiatrist, The Royal Melbourne Hospital	Victoria, Australia	Dr. Ramon Mocellin is a Consultant Psychiatrist at Delmont Private Hospital in Melbourne, where he specializes in aged psychiatry, dementia, and neuropsychiatry. He also holds a position at the Neuropsychiatry Unit at the Royal Melbourne Hospital, focusing on complex neuropsychiatric conditions. He has received recognition for his contributions to psychiatric care, notably in aged and neuropsychiatry, and has been actively involved in research, contributing to numerous publications and book chapters.

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