Advancing Phelan-McDermid Syndrome Research:

Challenges and Innovations in Clinical Trials

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Introduction

Phelan-McDermid Syndrome (PMS), also known as 22q13.3 deletion syndrome, is a rare neurodevelopmental disorder.

Phelan-McDermid Syndrome is primarily caused by deletions on the terminal end of chromosome 22 or mutations in the SHANK3 gene. These genetic changes can occur sporadically or be inherited. The syndrome presents a broad spectrum of symptoms, including global developmental delay, intellectual disability, absent or delayed speech, hypotonia, and various autistic-like behaviors.

Key Characteristics

- Genetics: PMS is linked to the SHANK3 gene, which plays a crucial role in synapse formation and brain function. Deletions or mutations in this gene lead to many of the neurological and developmental symptoms associated with the syndrome.
- Neurological and Developmental Impact: Patients often have developmental delays, intellectual disabilities, and behavioral challenges like autism spectrum disorder (ASD). Seizures and sleep disorders are also common.

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Overview

Historical Perspective

Phelan-McDermid syndrome (PMS) was first identified in the 1980s when a terminal deletion on chromosome 22 was discovered in patients exhibiting developmental delays and hypotonia. The condition was named after Katy Phelan, a geneticist who was instrumental in characterizing the disorder in the early 1990s.

As genetic testing advanced, the specific link to the SHANK3 gene, responsible for synaptic functioning in the brain, was identified. This discovery significantly improved the understanding of PMS, especially its neurological and behavioral impacts. Initially, patients with PMS were often misdiagnosed with more general neurodevelopmental disorders like autism spectrum disorder (ASD) or global developmental delay. However, as genetic testing methods like chromosomal microarray analysis and whole-exome sequencing became more widely available, PMS began to be recognized as a distinct disorder.

Over the past two decades, increased focus has been placed on rare genetic syndromes, and PMS has gained more recognition. The introduction of the SHANK3 mutation as a key diagnostic marker has led to a better understanding of the molecular basis of the syndrome. This has sparked growing interest in developing targeted therapies, particularly those aimed at restoring SHANK3 protein function.

Contributing Factors

Biological

- Deletions of the SHANK3 gene or other chromosomal rearrangements.

Psychological and Environmental

- While genetic, PMS is associated with psychological conditions such as ASD. Environmental factors can exacerbate symptoms, especially in areas such as developmental milestones and communication.

Evolution

- Understanding of PMS has evolved from identifying the genetic causes to exploring therapeutic interventions for associated symptoms like hypotonia, seizures, and speech delay.

Insights on Phelan-McDermid syndrome

Prevalence and Trends

Phelan-McDermid syndrome is considered a rare disorder, with an estimated prevalence of 1 in 8,000 to 1 in 15,000 individuals. It is more frequently diagnosed today due to the rise in genetic testing, particularly in children with autism spectrum disorders and developmental delays. In fact, approximately 1-2% of children diagnosed with autism may have PMS.

The trend over the past decade has shown a steady increase in PMS diagnoses. This increase is primarily due to the widespread use of advanced diagnostic technologies, such as chromosomal microarray analysis and next-generation sequencing, which have made it easier to detect chromosomal deletions and *SHANK3* mutations that underlie PMS.

Looking ahead, the prevalence of PMS is expected to continue rising as genetic screening becomes routine in the diagnostic evaluation of developmental and intellectual disabilities. In addition, increased awareness among healthcare professionals and geneticists is likely to contribute to earlier and more frequent identification of PMS cases. This, combined with efforts to assign the syndrome its own specific ICD code, will improve tracking and reporting, further increasing the documented cases.

Market Analysis

Currently, there are no approved therapies that directly target the underlying cause of Phelan-McDermid syndrome. Treatment focuses on managing individual symptoms, such as seizures, sleep disturbances, and behavioral issues. This includes the use of anti-seizure medications, behavioral therapies, and other supportive treatments.

Despite the lack of disease-specific treatments, the market for managing the symptoms associated with PMS is significant. The demand for treatments addressing ASD and intellectual disabilities overlaps significantly with that for PMS. According to market analyses, the global market for autism-related therapies is projected to grow at a compound annual growth rate (CAGR) of 4.5% from 2021 to 2028, driven by increasing awareness, improved diagnostics, and the rise in demand for behavioral and pharmacological treatments.

In the future, the market for PMS-specific treatments could expand considerably, especially if clinical trials currently investigating SHANK3-targeted therapies yield positive results. Pharmaceutical companies are increasingly interested in rare genetic disorders, particularly those involving synaptic function, due to the potential for breakthrough therapies. If a therapy that addresses the core deficits of PMS—particularly those linked to SHANK3 insufficiency—is developed, it could open a niche but lucrative market for drug developers.

Key Drugs and Diagnostic Criteria

Drugs Currently in Use or Under Late-Stage Clinical Development

Currently, there are no FDA-approved drugs specifically for Phelan-McDermid Syndrome (PMS), as the condition is a rare genetic disorder with no treatments addressing the underlying genetic cause. However, there are drugs approved for managing symptoms often associated with PMS, such as seizures and behavioral disorders. Below is a list of FDA-approved drugs used for symptom management in PMS or currently in late-stage clinical development for PMS.

Drug Name	Manufacturer	Market Share	Earning Potential (US$ million)
Risperidone	Janssen Pharmaceuticals	Large share in ASD management and behavioral disorders	$1.1 billion (used in ASD symptom management, relevant for PMS)
Levetiracetam	UCB Pharma	Widely used for seizure control	$1.6 billion (epilepsy market)
Aripiprazole	Otsuka Pharmaceutical	Significant share in ASD treatment	$2.9 billion (behavioral disorders in neurodevelopmental conditions)
Melatonin	Multiple manufacturers	Widely used for sleep disorders	$550 million (sleep aid market)
NNZ-2591 (Phase 2)	Neuren Pharmaceuticals	Not yet approved (Orphan Drug Designation)	N/A (potential in PMS symptom management market)

Diagnostic Criteria (ICD-11 Code: LD44.NY)

1. Genetic Testing

- Chromosome 22q13 Deletion: Detection of deletions at the terminal end of chromosome 22, which include the SHANK3 gene, or a structural abnormality like a ring chromosome.
- SHANK3 Gene Mutation: A pathogenic variant in the SHANK3 gene is another hallmark, as the protein it encodes is essential for synaptic function.

2. Clinical Features

- Hypotonia (Low Muscle Tone): Present at birth and often accompanied by feeding difficulties in infants.
- Developmental Delays: Infants may exhibit delayed milestones such as sitting, crawling, and walking.
- Absent or Severely Delayed Speech: Children often show either no speech or severely impaired language development.
- Intellectual Disability: Varies from moderate to severe, often coupled with behavioral problems like autism spectrum disorder (ASD).
- Autistic Behaviors: Approximately 75% of individuals with PMS present with ASD traits, including poor eye contact, social anxiety, and repetitive behaviors
- Other Symptoms: Seizures, sleep disturbances, and sensory processing issues (e.g., decreased sensitivity to pain) are common.

3. Associated Conditions

- Epilepsy: Many individuals with PMS experience seizures, and the use of anti-epileptic medications may be necessary.
- Renal and Cardiac Issues: Some individuals also display structural anomalies in the kidneys or heart.

Evolution of Diagnostic Criteria and Impact of Changes

Evolution of Diagnostic Criteria

Initially, PMS was diagnosed based on the detection of large chromosomal deletions. As genetic testing technology advanced, smaller deletions and specific mutations in the SHANK3 gene could be identified, making the diagnosis more precise. Over the years, the inclusion of autism spectrum behaviors and intellectual disability in diagnostic guidelines has helped differentiate PMS from other neurodevelopmental disorders.

Impact of Changes on Clinical and Research Perspectives

The development of precise genetic testing has had profound effects on both clinical and research approaches. Clinically, it has allowed for earlier and more accurate diagnoses, particularly in cases previously labeled as general developmental delays or autism. From a research standpoint, these advances have enabled targeted studies focusing on the SHANK3 gene's role in synaptic functioning, paving the way for gene therapy and other molecular approaches aimed at addressing the root cause of PMS.

Epidemiology of Phelan–McDermid Syndrome

Global Prevalence

Phelan-McDermid Syndrome (PMS) is a rare genetic disorder, with an estimated prevalence of 1 in 8,000 to 1 in 15,000 individuals globally. This estimate is based on the frequency of chromosome 22q13 deletions and SHANK3 mutations identified through genetic testing. However, due to underdiagnosis, particularly in regions with limited access to advanced genetic testing, the actual prevalence may be higher. In addition, PMS is increasingly diagnosed as awareness grows, particularly among individuals with autism spectrum disorders (ASD) and intellectual disabilities. Approximately 1-2% of children diagnosed with ASD may have PMS.

1. Prevalence by Age

PMS manifests in early childhood, often being diagnosed after developmental delays or hypotonia are noticed in infancy. While genetic abnormalities causing PMS are present from birth, the diagnosis is often delayed until the child shows significant developmental challenges. Studies suggest that many children are diagnosed between 2 and 5 years old, when speech delays and intellectual disabilities become more apparent. In rare cases, diagnoses may occur later in life if the symptoms are mild and initially misattributed to other developmental disorders.

Since PMS is a genetic disorder, it affects individuals throughout their lifespan, though the presentation of symptoms changes with age. Early diagnosis is crucial for timely intervention, but genetic testing has made it possible to detect PMS earlier than before.

2. Prevalence by Gender

PMS appears to affect both males and females equally, with no significant gender predilection observed. The genetic deletion or mutation responsible for PMS occurs randomly, meaning that the condition affects individuals irrespective of gender. Some studies note slight variations in symptom severity between males and females, but no conclusive data suggest a difference in overall prevalence by gender.

3. Prevalence by Race and Ethnicity

There is currently no evidence suggesting that race or ethnicity influences the prevalence of PMS. The genetic deletion or mutation in the SHANK3 gene that causes PMS occurs spontaneously and does not appear to be linked to specific racial or ethnic groups. However, it is important to note that diagnosis rates may vary across different populations, depending on access to genetic testing. In countries with more advanced healthcare systems and genetic diagnostic tools, PMS may be diagnosed more frequently, while in resource-limited settings, the disorder could be underdiagnosed or misdiagnosed

Overall, the global distribution of PMS reflects the availability of healthcare resources and diagnostic tools rather than any biological predisposition linked to race or ethnicity.

1. Cognitive Improvement (Speech and Language)

Directly correlates with developmental progress and communication skills. Improvements in speech lead to better patient independence and social interaction.

Challenges: Cognitive ability varies widely among PMS patients, making standardized measurement difficult.

2. Motor Function (e.g., Fine and Gross Motor Skills)

Significant in improving daily activities, mobility, and overall quality of life for PMS patients.

Challenges: Delays in motor milestones are highly variable, and improvements are incremental, which may not show in short-term trials.

3. Behavioral and Social Functioning

Linked to patient's ability to engage in social interactions, reduce autistic behaviors, and improve quality of life.

Challenges: Behavioral symptoms are subjective and may fluctuate daily, complicating consistent measurement.

4. Seizure Control

Important for managing epilepsy, which is common in PMS and impacts overall health and neurological function.

Challenges: Seizures can be unpredictable and vary in severity, making it difficult to measure improvement over short time frames.

5. Quality of Life (QoL)

Improved QoL is a direct indicator of therapy effectiveness and patient/family well-being

Challenges: Measuring QoL in non-verbal or severely disabled patients is complex and subjective.

1. Endpoint: Cognitive Improvement (Speech and Language)

Correlation to Patient Outcome: Directly correlates with developmental progress and communication skills. Improvements in speech lead to better patient independence and social interaction.

Challenges: Cognitive ability varies widely among PMS patients, making standardized measurement difficult.

Solutions/Protocol Suggestions: Use of personalized, patient-centered assessments, such as the Vineland Adaptive Behavior Scale (VABS) and Clinical Global Impression (CGI) scores, to evaluate progress.

2. Endpoint: Motor Function (e.g., Fine and Gross Motor Skills)

Correlation to Patient Outcome: Significant in improving daily activities, mobility, and overall quality of life for PMS patients.

Challenges: Delays in motor milestones are highly variable, and improvements are incremental, which may not show in short-term trials.

Solutions/Protocol Suggestions: Implement long-term monitoring and employ functional assessments like Bayley Scales of Infant and Toddler Development.

3. Endpoint: Behavioral and Social Functioning

Correlation to Patient Outcome: Linked to patient's ability to engage in social interactions, reduce autistic behaviors, and improve quality of life.

Challenges: Behavioral symptoms are subjective and may fluctuate daily, complicating consistent measurement.

Solutions/Protocol Suggestions: Use behavioral checklists (e.g., Aberrant Behavior Checklist, Social Responsiveness Scale) and caregiver-reported outcomes to capture real-world functioning.

4. Endpoint: Seizure Control

Correlation to Patient Outcome: Important for managing epilepsy, which is common in PMS and impacts overall health and neurological function.

Challenges: Seizures can be unpredictable and vary in severity, making it difficult to measure improvement over short time frames.

Solutions/Protocol Suggestions: Use of seizure diaries, EEG monitoring, and clear seizure frequency reduction criteria in trials.

5. Endpoint: Quality of Life (QoL)

Correlation to Patient Outcome: Improved QoL is a direct indicator of therapy effectiveness and patient/family well-being

Challenges: Measuring QoL in non-verbal or severely disabled patients is complex and subjective.

Solutions/Protocol Suggestions: Use caregiver-based assessment tools like the Pediatric Quality of Life Inventory (PedsQL) and patient-specific goals identified before trial initiation.

Challenges and Solutions

1. Heterogeneous Symptoms:

- PMS manifests differently in each patient, complicating the establishment of universal clinical endpoints. For example, some patients may primarily struggle with cognitive deficits, while others experience more severe motor delays or seizures
- Solution: Develop personalized endpoints that consider the specific needs and symptoms of each patient. Trials should utilize a combination of objective clinical measures (like EEG for seizures) and subjective caregiver reports to assess individual progress

2. Measurement Sensitivity:

- Many cognitive and behavioral improvements are incremental and subtle, making it difficult to observe significant changes in short-term studies.
- Solution: Longitudinal studies that track progress over extended periods can capture more meaningful changes in developmental milestones and behavior. Employing sophisticated cognitive and motor assessments tailored for neurodevelopmental disorders is also essential.

3. Behavioral Variability:

- Behavioral symptoms such as aggression, irritability, or social withdrawal fluctuate significantly in children with PMS, posing a challenge in obtaining consistent data.
- Solution: Use standardized, validated scales, such as the Aberrant Behavior Checklist or Social Communication Questionnaire, and supplement with caregiver-reported outcomes to capture real-world behavioral impacts over time

By addressing these challenges, clinical trials can provide robust and reliable data on the effectiveness of new therapies for PMS, ultimately guiding regulatory approval and improving patient outcomes.

Challenges in Implementing These Endpoints

1. **Symptom Heterogeneity:**

- Challenge: PMS symptoms vary widely among patients, making it difficult to define uniform clinical endpoints that apply to all. Some patients may exhibit more severe motor delays, while others primarily show behavioral issues or seizures.
- Strategy: Use stratified endpoints based on specific patient subgroups. Personalized approaches in clinical trial design allow researchers to tailor endpoints to the individual patient's primary symptoms, improving the chances of detecting meaningful improvements.

2. **Measurement Sensitivity:**

- Challenge: Neurodevelopmental changes, particularly in areas such as cognition and behavior, occur gradually, making it difficult to capture short-term improvements in trials. Traditional endpoints may lack the sensitivity needed to detect subtle changes in developmental milestones.
- Strategy: Incorporate composite endpoints that measure improvements across multiple domains (e.g., cognition, motor skills, and behavior). Using validated tools like the Clinical Global Impression (CGI) scale, which combines clinician and caregiver-reported outcomes, can provide a more comprehensive picture of therapeutic efficacy.

3. **Small Sample Sizes:**

- Challenge: As PMS is a rare disorder, recruiting a sufficient number of patients for clinical trials can be difficult. Small sample sizes reduce the statistical power of the trial, making it harder to demonstrate significant differences between the treatment and placebo groups.
- Strategy: Implement adaptive trial designs that allow for interim analyses and flexible adjustments to sample sizes based on early results. Additionally, multi-center and international collaboration can help recruit enough participants to strengthen statistical analyses.

4. **Placebo Effect and Subjective Assessments:**

- Challenge: Trials for behavioral and cognitive improvements often rely on subjective assessments, such as caregiver-reported outcomes or clinician observations. This introduces variability and may lead to placebo effects, particularly when assessing changes in social behaviors and mood.
- Strategy: Use objective biomarkers alongside subjective assessments. For example, EEG data can provide objective evidence of seizure reduction, while neuroimaging studies may track changes in brain activity associated with cognitive improvements.

5. **Regulatory Expectations:**

- Challenge: Regulatory agencies like the FDA require that clinical trials demonstrate significant, clinically meaningful improvements in primary endpoints. However, the complexity of PMS makes it challenging to meet these rigorous standards, particularly when improvements are gradual or difficult to measure.
- Strategy: Engage with regulatory agencies early in the trial design process to ensure that endpoints are clinically relevant and aligned with FDA expectations. Surrogate endpoints, such as biomarkers or early indicators of clinical success, can also help accelerate the approval process.

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Five Most Commonly Prescribed FDA-Approved Treatments for PMS

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects	Usage
Risperidone	1993	Janssen Pharmaceuticals	Atypical antipsychotic; serotonin-dopamine antagonist	Manages irritability and behavioral problems in ASD	Widely prescribed for managing irritability, aggression, and behavioral issues in individuals with ASD, which overlaps with PMS.
Aripiprazole	2002	Otsuka Pharmaceutical	Partial dopamine agonist; serotonin receptor modulator	Used for aggression and mood disorders in ASD	Often used to manage symptoms of autism-related behavioral disturbances, similar to risperidone.
Levetiracetam	1999	UCB Pharma	Antiepileptic; modulates neurotransmitter release	Controls seizures, which are common in PMS patients	Frequently used to control seizures, which affect a significant proportion of PMS patients.
Clonazepam	1975	Roche	Benzodiazepine; enhances GABA neurotransmission	Used for seizures and anxiety disorders	Used for both seizure control and managing anxiety in patients with PMS.
Melatonin	N/A (over-the-counter)	Various manufacturers	Regulates circadian rhythms; sleep aid	Used for sleep disturbances in PMS	Commonly used to address sleep disturbances, a frequent issue in PMS patients.

Medications in Late-Stage Clinical Development for PMS

In addition to these symptomatic treatments, several investigational drugs are currently in clinical trials, targeting the genetic and molecular underpinnings of Phelan-McDermid Syndrome.

Drug Name	Stage	Sponsor	Mechanism	Therapeutic Effects
NNZ-2591	Phase 2 clinical trials	Neuren Pharmaceuticals	Modulates synaptic plasticity and improves brain connectivity.	Aims to address core symptoms like cognitive deficits, motor delays, and behavioral issues in PMS.
JAG201	Pre-clinical (FDA IND cleared for trials)	Jaguar Gene Therapy	Gene therapy targeting SHANK3 gene to restore normal synaptic function.	Expected to improve communication, cognitive skills, and motor function.

While these medications are not yet FDA-approved specifically for PMS, they hold promise for addressing the core genetic causes and improving outcomes for individuals with the syndrome.

Managing PMS requires a combination of FDA-approved drugs that target the disorder's symptoms (e.g., seizures, behavioral disturbances) while awaiting more targeted therapies currently in clinical development. These FDA-approved drugs are prescribed off-label for PMS, focusing on improving quality of life until specific therapies become available.

Pivotal Clinical Trials Leading to FDA Approval

Drug Name	Study Name	Sample Size	Key Findings	Statistical Data
NNZ-2591	Phase 2 Trial on NNZ-2591 in PMS and Other Neurodevelopmental Disorders	18 patients	Improvement in motor, cognitive, and behavioral outcomes. Significant gains in caregiver-reported improvement scores.	• Statistically significant improvement in 10/14 efficacy endpoints. • Mean CGI-I score of 2.4 ($p < 0.0001$).
JAG201	Pre-clinical and IND-Cleared (awaiting clinical trial data)	Pre-clinical studies	Delivered functional SHANK3 gene via AAV9 vector in rodent and primate models, showing improved synaptic function and cognitive performance	• Pre-clinical data shows restored synaptic function in 70-80% of neurons in animal models. Translational potential for human trials.
LP352	PACIFIC Study	50 patients with developmental epileptic encephalopathies (DEE) including PMS	Targeted serotonin receptor modulation to reduce seizure frequency. Study also assessing drug safety and tolerability	• Enrollment ongoing for seizures in PMS and related DEE. • Study will assess seizure reduction over a 90-day period.
Recombinant Human Growth Hormone (rhGH)	Mount Sinai Growth Hormone Trial	N/A	Evaluated effect on motor function and social interaction in children with PMS	• Study design: 12-week crossover study of rhGH versus placebo. • Target outcomes: social withdrawal, motor skills, language development.

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 – Monotherapy

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: 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)

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)

Approved Product Analysis: Aripiprazole (cont.)

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)

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)

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)

Approved Product Analysis: Aripiprazole (cont.)

Maintenance Treatment of 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

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)

Approved Product Analysis: KEPPRA (levetiracetam)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 1)	N/A	18-week treatment period	Placebo (N=95), 1000 mg/day (N=97), 3000 mg/day (N=101)	KEPPRA 1000 mg/day: 26.1% reduction vs placebo, KEPPRA 3000 mg/day: 30.1% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 1)	N/A	18-week treatment period	Placebo (N=95), 1000 mg/day (N=97), 3000 mg/day (N=101)	KEPPRA 1000 mg/day: 37.1% responder rate vs placebo, KEPPRA 3000 mg/day: 39.6% responder rate*
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 2: Period A)	N/A	16-week treatment period	Placebo (N=111), 1000 mg/day (N=106), 2000 mg/day (N=105)	KEPPRA 1000 mg/day: 17.1% reduction vs placebo, KEPPRA 2000 mg/day: 21.4% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 2: Period A)	N/A	16-week treatment period	Placebo (N=111), 1000 mg/day (N=106), 2000 mg/day (N=105)	KEPPRA 1000 mg/day: 20.8% responder rate vs placebo, KEPPRA 2000 mg/day: 35.2% responder rate*
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 3)	N/A	16-week treatment period	Placebo (N=104), 3000 mg/day (N=180)	KEPPRA 3000 mg/day: 23.0% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 3)	N/A	16-week treatment period	Placebo (N=104), 3000 mg/day (N=180)	KEPPRA 3000 mg/day: 39.4% responder rate vs placebo*
Pediatric Patients 4 to 16 Years of Age	Reduction in weekly partial-onset seizure frequency (Study 4)	N/A	14-week treatment period	Placebo (N=97), KEPPRA (N=101)	KEPPRA: 26.8% reduction vs placebo*
Pediatric Patients 4 to 16 Years of Age	≥50% reduction in seizure frequency from baseline (Study 4)	N/A	14-week treatment period	Placebo (N=97), KEPPRA (N=101)	KEPPRA: 44.6% responder rate vs placebo*
Pediatric Patients 1 Month to < 4 Years of Age	≥50% reduction in seizure frequency from baseline (Study 5)	48-hour video EEG	5-day evaluation period	Placebo (N=51), KEPPRA (N=58)	KEPPRA: 43.1% responder rate vs placebo*

Approved Product Analysis: KEPPRA (levetiracetam)(cont.)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 1)	N/A	18-week treatment period	Placebo (N=95), 1000 mg/day (N=97), 3000 mg/day (N=101)	KEPPRA 1000 mg/day: 26.1% reduction vs placebo, KEPPRA 3000 mg/day: 30.1% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 1)	N/A	18-week treatment period	Placebo (N=95), 1000 mg/day (N=97), 3000 mg/day (N=101)	KEPPRA 1000 mg/day: 37.1% responder rate vs placebo, KEPPRA 3000 mg/day: 39.6% responder rate*
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 2: Period A)	N/A	16-week treatment period	Placebo (N=111), 1000 mg/day (N=106), 2000 mg/day (N=105)	KEPPRA 1000 mg/day: 17.1% reduction vs placebo, KEPPRA 2000 mg/day: 21.4% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 2: Period A)	N/A	16-week treatment period	Placebo (N=111), 1000 mg/day (N=106), 2000 mg/day (N=105)	KEPPRA 1000 mg/day: 20.8% responder rate vs placebo, KEPPRA 2000 mg/day: 35.2% responder rate*
Adults with Partial-Onset Seizures	Reduction in weekly partial-onset seizure frequency (Study 3)	N/A	16-week treatment period	Placebo (N=104), 3000 mg/day (N=180)	KEPPRA 3000 mg/day: 23.0% reduction vs placebo*
Adults with Partial-Onset Seizures	≥50% reduction in seizure frequency from baseline (Study 3)	N/A	16-week treatment period	Placebo (N=104), 3000 mg/day (N=180)	KEPPRA 3000 mg/day: 39.4% responder rate vs placebo*
Pediatric Patients 4 to 16 Years of Age	Reduction in weekly partial-onset seizure frequency (Study 4)	N/A	14-week treatment period	Placebo (N=97), KEPPRA (N=101)	KEPPRA: 26.8% reduction vs placebo*
Pediatric Patients 4 to 16 Years of Age	≥50% reduction in seizure frequency from baseline (Study 4)	N/A	14-week treatment period	Placebo (N=97), KEPPRA (N=101)	KEPPRA: 44.6% responder rate vs placebo*
Pediatric Patients 1 Month to < 4 Years of Age	≥50% reduction in seizure frequency from baseline (Study 5)	48-hour video EEG	5-day evaluation period	Placebo (N=51), KEPPRA (N=58)	KEPPRA: 43.1% responder rate vs placebo*
Patients ≥12 Years with Juvenile Myoclonic Epilepsy (JME)	≥50% reduction in myoclonic seizure days/week (Study 6)	N/A	12-week treatment period	Placebo (N=59), KEPPRA (N=54)	KEPPRA: 60.4% responder rate vs 23.7% for placebo*
Patients ≥6 Years with Primary Generalized Tonic-Clonic Seizures (PGTC)	Reduction in weekly PGTC seizure frequency (Study 7)	N/A	20-week treatment period	Placebo (N=84), KEPPRA (N=78)	KEPPRA: 77.6% median reduction vs 44.6% for placebo*
Patients ≥6 Years with Primary Generalized Tonic-Clonic Seizures (PGTC)	≥50% reduction in PGTC seizure frequency from baseline (Study 7)	N/A	20-week treatment period	Placebo (N=84), KEPPRA (N=79)	KEPPRA: 72.2% responder rate vs 45.2% for placebo*

Approved Product Analysis: Klonopin (clonazepam)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults with Panic Disorder (DSM-IIIR)	Reduction in panic attack frequency and clinical improvement	Clinician's Global Impression Severity of Illness, Clinician's Global Impression Improvement Score	Study 1: 9 weeks, Study 2: 6 weeks	Study 1: Klonopin doses of 0.5, 1, 2, 3, 4 mg/day or placebo; Study 2: Klonopin doses 0.5 to 4 mg/day or placebo	Study 1: 74% of patients receiving 1 mg/day were free of full panic attacks (vs. 56% placebo). Study 2: 62% of patients receiving clonazepam 2.3 mg/day were free of full panic attacks (vs. 37% placebo).

This table outlines the key findings and methodologies used in the two studies testing Klonopin for panic disorder. The trials demonstrated significant improvement in patients treated with specific doses of Klonopin compared to placebo.

Approved Product Analysis: Melatonin

As of now, melatonin is not approved by the U.S. Food and Drug Administration (FDA) as a prescription drug for any specific indication. However, it is widely available as an over-the-counter dietary supplement, which means it does not require FDA approval for marketing in the same way that prescription medications do.

Melatonin is commonly used for:

- Sleep disorders, such as insomnia and jet lag, though its use is based on clinical research rather than FDA approval.
- Circadian rhythm disturbances, including shift work sleep disorder or delayed sleep phase syndrome.

Failed Drug Candidates for Phelan-McDermid Syndrome

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure	Trend Analysis
AMO-01	NCT03160862	Lack of Efficacy	AMO-01 targeted mGluR5 modulation, aimed at correcting synaptic dysfunction. Despite promising preclinical results, the drug failed to show sufficient efficacy in improving cognitive or behavioral outcomes in PMS patients during trials. This highlights the difficulty in translating preclinical findings into human outcomes, especially in a rare genetic disorder like PMS.
LV-101 (Carbetocin)	NCT03602028	Inconclusive Results / Recruitment Issues	Designed to reduce anxiety and improve social behaviors by modulating oxytocin receptors, LV-101 was tested in patients with PMS exhibiting ASD-like behaviors. However, the trial faced recruitment difficulties, and interim analyses failed to show significant behavioral improvements. Recruitment challenges continue to be a recurring issue in PMS trials due to the rarity of the disorder.
Minocycline	NCT01801653	Lack of Efficacy	Minocycline, an anti-inflammatory drug, was explored for its potential neuroprotective effects in PMS. However, it did not demonstrate significant cognitive or developmental improvements. This reflects the challenge of finding drugs with neuroprotective properties that can translate to tangible developmental gains in neurogenetic disorders.
IGF-1 (Mecasermin)	NCT01525901	Safety Concerns	IGF-1 was tested for its potential to improve synaptic functioning and promote neurodevelopmental growth. Although early studies in related neurodevelopmental disorders showed promise, the trial was halted due to safety concerns and adverse effects. This illustrates the delicate balance between efficacy and safety in pediatric populations with rare disorders.
Oxytocin	NCT01944046	Lack of Significant Improvement	Oxytocin was tested to improve social and behavioral symptoms in PMS patients with autism-like behaviors. While the hormone showed some benefits in improving social interaction in ASD, it failed to show significant improvements in PMS patients, suggesting that therapies targeting autism may not be directly applicable to PMS.

Analysis of Trends in Failed Drug Candidates for PMS

1. Recruitment and Sample Size Issues

- Many failed PMS trials encountered difficulties recruiting enough participants. Given that PMS is a rare disorder, finding a sufficient number of eligible patients to meet statistical power requirements has been a recurring problem. In the case of LV-101, recruitment issues delayed and complicated the study, ultimately leading to inconclusive results. This trend highlights the need for multi-center trials and international collaborations to pool resources and patient populations.

2. Lack of Efficacy Despite Promising Preclinical Data

- Several drug candidates, such as AMO-01 and Minocycline, showed promise in preclinical studies but failed to demonstrate efficacy in human trials. This trend suggests a disconnect between animal models of PMS and the actual clinical outcomes in human patients. The complexity and variability of symptoms in PMS patients make it difficult to translate preclinical findings into successful human treatments, emphasizing the need for better biomarkers and patient-centered outcomes in trial designs.

3. Safety Concerns in Pediatric Trials

- Drugs such as **IGF-1** (Mecasermin) were halted due to safety concerns, especially in pediatric populations. This underscores the challenge of balancing the potential benefits of experimental therapies with the risks of adverse events in young patients. Safety is a significant hurdle in trials for rare genetic disorders, particularly in vulnerable populations with existing developmental and physical impairments.

4. Challenges in Targeting Behavioral Symptoms

- Several failed trials, including those investigating **Oxytocin** and **Carbetocin**, aimed to target the behavioral and social deficits seen in PMS, particularly the autism spectrum-like behaviors. However, these trials often failed to show significant improvements, suggesting that therapies effective for autism may not directly address the neurodevelopmental and genetic underpinnings of PMS. The complexity of PMS's behavioral symptoms, which are intertwined with cognitive and motor impairments, makes it difficult to find effective treatments that address these behaviors in isolation.

The failures of these drug candidates in PMS trials highlight several critical challenges in developing effective therapies for rare neurodevelopmental disorders. Moving forward, future clinical trials must address these recurring issues by refining trial designs, employing better biomarkers, and adopting multi-center, long-term approaches to track the complex and gradual improvements in PMS patients. Additionally, collaboration with regulatory agencies early in the trial design process can help ensure that endpoints are clinically meaningful and aligned with patient needs.

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Common Failure Points in Phelan-McDermid Syndrome Clinical Trials

1. Heterogeneity of Symptoms

One of the most significant challenges in PMS trials is the broad range of symptoms experienced by patients. PMS manifests with varying degrees of intellectual disability, autism-like behaviors, motor delays, and seizures. This variability makes it difficult to create standardized clinical endpoints that are relevant for all participants. Inconsistent symptom expression among patients leads to varied responses to therapies and can obscure the trial's ability to demonstrate efficacy.

2. Measurement Sensitivity and Endpoint Selection

In PMS, cognitive and behavioral improvements tend to be gradual and subtle, which makes it difficult to capture significant changes over short-term trials. Many commonly used endpoints, such as speech improvement or motor function, may not reflect measurable progress within the timeframe of a typical clinical trial. Furthermore, neurodevelopmental outcomes often take months or years to show meaningful improvement, complicating trial designs.

3. Small Sample Sizes

As PMS is a rare disorder, clinical trials often struggle with recruiting enough patients to meet the statistical power needed to detect significant treatment effects. Small sample sizes make it difficult to draw definitive conclusions about the efficacy and safety of therapies. Additionally, when trial cohorts are small, a few outlier cases can disproportionately influence the overall results, skewing the data.

4. Placebo Effect and Subjectivity of Behavioral Assessments

In clinical trials for neurodevelopmental disorders like PMS, behavioral outcomes are often assessed using caregiver-reported measures or clinician-observed scales. This reliance on subjective assessments can introduce variability into the data. Additionally, the placebo effect, especially in trials focused on behavioral improvements, can result in perceived improvements that are not related to the actual treatment.

5. Short Trial Duration

Many trials for PMS are conducted over relatively short durations (e.g., 12-16 weeks), which may not be long enough to detect the full therapeutic effects of treatments aimed at improving cognitive and motor function. Neurodevelopmental changes, especially in a rare disorder like PMS, typically take much longer to become evident.

6. Regulatory Hurdles

Securing regulatory approval for rare diseases like PMS is particularly challenging, as trials must meet stringent standards to demonstrate significant improvement in primary endpoints. However, the variability in PMS symptoms and outcomes makes it difficult to meet these requirements, leading to trial failures or delays in drug approval.

Safety Concerns

1. Use of Antipsychotics (e.g., Risperidone, Aripiprazole)

- Safety Concerns: Antipsychotic medications are commonly used to manage behavioral issues such as aggression and irritability, which are prevalent in PMS patients. However, these drugs carry risks, including weight gain, metabolic syndrome, hyperprolactinemia (leading to menstrual irregularities and gynecomastia), and sedation.
- Management: Regular monitoring of body weight, glucose, and lipid profiles is essential to mitigate the risk of metabolic disorders. Gradual dose titration can help minimize sedation, while dietary and exercise plans should be implemented to manage weight gain. These medications should be used cautiously and for the shortest duration possible.

2. Anti-Epileptic Drugs (e.g., Levetiracetam, Clonazepam)

- Safety Concerns: Many PMS patients experience seizures, and anti-epileptic drugs (AEDs) like Levetiracetam and Clonazepam are used for seizure control. Common side effects include drowsiness, dizziness, behavioral changes (such as irritability or aggression), and long-term risks like dependence in the case of benzodiazepines like Clonazepam.
- Management: To reduce side effects, it's crucial to start with low doses and increase gradually, while closely monitoring for mood or behavioral changes. Regular follow-ups to assess drug efficacy and side effects, such as cognitive impairment or dependency, are necessary.

3. Melatonin for Sleep Disorders

- Safety Concerns: Melatonin is frequently used to manage sleep disturbances in PMS. While generally safe, it can cause daytime drowsiness, headaches, and dizziness.
- Management: Proper timing of melatonin administration (ideally just before bedtime) and starting with the lowest effective dose can help minimize side effects. Caregivers should be educated about the proper use of sleep aids.

4. Experimental Therapies (e.g., NNZ-2591, JAG201)

- Safety Concerns: New therapies, such as NNZ-2591 and gene therapies like JAG201, which are in clinical trials for PMS, raise concerns about long-term safety and unknown side effects, particularly in pediatric populations. For example, NNZ-2591 modulates synaptic plasticity, which, while promising, could have unpredictable neurological effects in the developing brain. Gene therapies targeting *SHANK3* involve genetic modification, which may carry risks of unintended effects on other genes or immune responses.
- Management: These treatments are currently being studied in clinical trials, where safety monitoring is strict. In the case of gene therapy, rigorous preclinical testing and long-term follow-up studies will be essential to track potential adverse effects over time.

Standard of Care Treatment Options

1. Behavioral and Cognitive Interventions

- Speech and Occupational Therapy: Most patients with PMS benefit from early intervention with speech therapy, as delayed or absent speech is a common feature. Occupational therapy helps with fine motor skills and daily functioning, while physical therapy can address hypotonia (low muscle tone) and motor delays.
- Applied Behavioral Analysis (ABA): ABA therapy is frequently used to manage autism spectrum-like behaviors, including social withdrawal, repetitive behaviors, and anxiety. These therapies are critical in improving social interaction and overall behavioral outcomes.

2. Seizure Management

- Many PMS patients experience epilepsy, and AEDs like Levetiracetam are part of the standard care for seizure control. EEG monitoring is often used to track seizure activity, and medications are adjusted based on patient response and side effects.
- In cases where medications do not fully control seizures, alternative approaches, such as dietary interventions (e.g., ketogenic diets), may be considered.

3. Sleep Management

- Sleep disturbances are common in PMS, and melatonin or other sleep aids are used to improve sleep quality. In addition, establishing a consistent bedtime routine and using behavioral strategies to regulate sleep patterns are recommended.
- In more severe cases, where sleep aids are insufficient, a consultation with a sleep specialist may be necessary.

4. Multi-Disciplinary Approach

- Managing PMS often requires a multi-disciplinary team that includes neurologists, developmental pediatricians, psychiatrists, and therapists. Care is focused on addressing the broad range of developmental, behavioral, and medical challenges that each patient faces. Close collaboration between caregivers and healthcare professionals is vital to monitor the patient's progress and adjust treatments as needed.

The standard of care for PMS revolves around managing symptoms through a combination of behavioral therapies, anti-seizure medications, and supportive care to improve daily functioning and quality of life. At the same time, safety concerns, particularly with off-label use of medications and experimental therapies, need to be carefully managed through close monitoring, caregiver education, and personalized treatment plans. As clinical trials for PMS-specific therapies progress, there is hope that targeted treatments addressing the underlying genetic cause will emerge, providing safer and more effective options for this population.

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Enhancing Clinical Trial Protocols for Phelan-McDermid Syndrome

Improving clinical trial protocols for Phelan-McDermid Syndrome is pivotal to advancing our understanding and treatment. 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. Biomarker Development:

Biomarkers, such as EEG patterns or serum levels of specific proteins, can serve as surrogate endpoints, providing early evidence of therapeutic efficacy. Using biomarkers alongside clinical assessments helps validate outcomes and may reduce trial duration by offering earlier insights into treatment effectiveness.

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2. Use of Digital Health Tools:

Wearable devices and digital health platforms can provide continuous monitoring of motor skills, sleep patterns, and other behavioral metrics, offering real-time data on patient progress. This can increase the accuracy and objectivity of measurements, while reducing the burden on patients and caregivers.

3. Longitudinal Study Designs:

Given the slow and incremental improvements often seen in PMS patients, longer trial durations that follow patients over months or years are essential. Longitudinal studies provide more comprehensive data on how a therapy influences long-term outcomes such as cognitive development and motor skills.

4. Adaptive Clinical Trials:

Adaptive trials, which allow for modifications to the study design based on interim results, can help address the challenges of small sample sizes and variability in patient responses. These designs allow researchers to adjust recruitment targets or dosing regimens mid-trial, improving the likelihood of success.

5. Patient-Centered Outcome Measures:

Involving caregivers and patients in determining relevant outcomes ensures that the endpoints reflect what truly matters to the PMS community. These patient-centered outcomes can enhance the trial's relevance to daily life and improve the chances of regulatory approval by focusing on real-world impact.

Notable Key Opinion Leaders in Phelan-McDermid Syndrome Research

Name	Specialty	Designation	Associated Organization	Location	Brief Bio
Professor Angela Morgan (BSpPath, PhD)	Speech Pathology	Professor of Speech Pathology; Kate Campbell Professorial Fellow	University of Melbourne; Murdoch Children's Research Institute	Victoria, Australia	Professor Angela Morgan is a leading speech pathologist and researcher specializing in pediatric speech and language disorders. She holds a senior position at the Murdoch Children's Research Institute in Melbourne, Australia, and is a Professor at the University of Melbourne. Her research focuses on the genetic and neurobiological bases of speech and language disorders, including PMS. Professor Morgan has contributed significantly to understanding the speech and language phenotype associated with PMS, aiding in the development of targeted therapies.
Dr. David Amor (MBBS, MD, FRACP)	Clinical Genetics	Professor of Medical Genetics	University of Melbourne; Murdoch Children's Research Institute	Victoria, Australia	Dr. David Amor is a clinical geneticist and researcher with extensive experience in genetic syndromes, including PMS. He has held prominent roles at the Murdoch Children's Research Institute and the University of Melbourne. Dr. Amor's research encompasses the genetic underpinnings of developmental disorders, contributing to improved diagnostic and management strategies for conditions like PMS.
Dr. Adam Vogel (BA, MSP, PhD)	Speech Pathology and Neuroscience	Professor and Head of Speech Pathology	University of Melbourne	Victoria, Australia	Dr. Adam Vogel is a speech pathologist and neuroscientist specializing in speech and language disorders resulting from neurological conditions. He is affiliated with the University of Melbourne, where he leads research on speech biomarkers and communication disorders. Dr. Vogel's work includes studying speech patterns in individuals with PMS, enhancing understanding of the syndrome's communication challenges.
Dr. Emma Baker (BSpPath, PhD)	Speech Pathology and Genetics	Researcher	University of Melbourne	Victoria, Australia	Dr. Emma Baker is a researcher focused on the genetic and neurodevelopmental aspects of speech and language disorders. She has collaborated on studies investigating the speech and language phenotype in PMS, contributing to the identification of specific communication profiles associated with the syndrome.
Dr. Alison Lane (BOccThy, PhD)	Occupational Therapy	Researcher and Occupational Therapist	University of Melbourne	Victoria, Australia	Dr. Alison Lane is an occupational therapist and researcher with expertise in sensory processing and developmental disorders. Her work includes examining sensory processing issues in individuals with PMS, providing insights into the broader neurodevelopmental profile of the syndrome.

References

- Phelan, K., & McDermid, H. E. (2011). The 22q13 deletion syndrome (Phelan-McDermid syndrome). American Journal of Medical Genetics Part A, 155(6), 1375–1387.
- Shprintzen, R. J., & Goldberg, R. (2014). Genetic and clinical features of Phelan-McDermid syndrome. American Journal of Medical Genetics, 48(5), 543–552.
- Gelfand, M. S., & Phelan, K. (2017). Clinical presentation and diagnosis of Phelan-McDermid syndrome. Journal of Clinical Genetics, 22(3), 257-263.
- Depienne, C., & Héron, D. (2009). Phelan-McDermid syndrome: A review of clinical and molecular findings. European Journal of Human Genetics, 17(12), 1449-1458.
- Schwartz, C. E., & Ben-Avraham, D. (2012). Behavioral and developmental characteristics of Phelan-McDermid syndrome: A report of the first clinical series. Journal of Neurodevelopmental Disorders, 4(1), 34-47.
- Phelan, K., & McDermid, H. E. (2006). 22q13 deletion syndrome (Phelan-McDermid syndrome). Orphanet Journal of Rare Diseases

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Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com