SYSTEMATIC REVIEW AND META-ANALYSIS OF PIMAVANSERIN AND VOLINANSERIN IN SCHIZOPHRENIA TREATMENT

by

Nylev Vargas-Cruz, BS

THESIS

Presented to the Faculty of

The University of Houston-Clear Lake

In Partial Fulfillment

Of the Requirements

For the Degree

MASTER OF SCIENCE

in Psychology

THE UNIVERSITY OF HOUSTON-CLEAR LAKE

MAY, 2022

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Nylev Vargas-Cruz

APPROVED BY

_____

Georgina Moreno, Ph.D., Chair

_____

David Malin, Ph.D., Committee Member

_____

Christopher Ward, Ph.D., Committee Member

RECEIVED/APPROVED BY THE COLLEGE OF HUMAN SCIENCES AND HUMANITIES:

_____

Samuel Lyndon Gladden, Ph.D., Associate Dean

_____

Glenn Sanford, Ph.D., Dean

ABSTRACT

SYSTEMATIC REVIEW AND META-ANALYSIS OF PIMAVANSERIN AND VOLINANSERIN IN SCHIZOPHRENIA TREATMENT

Nylev Vargas-Cruz
University of Houston-Clear Lake, 2022

Thesis Chair: Georgina Moreno, PhD

Schizophrenia is a severe mental disorder that affects 1% of the population. Despite its low prevalence, it is ranked among the top fifteen leading causes of disability worldwide. Antipsychotics targeting serotonergic receptors, specifically 5-HT_{2A} receptors, are being developed for schizophrenia treatment and continue to show promise. Pimavanserin and Volinanserin are two such atypical antipsychotics that are highly selective towards the 5-HT_{2A} receptor. In this study, we performed a systematic review and meta-analysis of Volinanserin (MDL-100907) and Pimavanserin (ACP-103) to evaluate the effectiveness of these drugs in the treatment of schizophrenia. A literature search was performed using Pub-Med, ClinicalTrials.gov, and Cochrane databases. Our search strategy consisted of the following strings: Pimavanserin or ACP-103 and Volinanserin or MDL-100907 and Schizophrenia or Schizophrenia spectrum. Based on comparable outcomes of measurement (i.e., PANSS, SGI, KSS, DAI-10), Pimavanserin is a safe adjunctive treatment. However, there is not enough data to conclude efficacy. These results provide

additional support for 5-HT_{2A} as a key component for the treatment of schizophrenia. Continued research is needed on the efficacy of Pimavanserin, Volinanserin, and other drugs that target 5-HT_{2A} receptors in the treatment of schizophrenia.

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CHAPTER I:

SCOPE OF THE PROBLEM

Schizophrenia is a severe mental disorder that affects 1% of the population. Despite its low prevalence, it is ranked among the top fifteen leading causes of disability worldwide (Charlson et al., 2018; Vos, 2017). The annual cost of schizophrenia treatment is found to be above $60 billion in the US, of which 50% to 85% represent indirect costs, including productivity losses related to morbidity and premature mortality (Chong et al., 2016). Therefore lack of effective treatment available for schizophrenia and high morbidity costs is reflected in sick leave, unemployment, and permanent disability (Chong et al., 2016).

The first FDA-approved drug for the treatment of Schizophrenia was Chlorpromazine which was introduced to the United States in the 1960s (Seeman, 2002). This drug is part of a group of drugs classified as typical or first-generation antipsychotics. These medications target dopamine receptors to diminish positive symptoms of schizophrenia, which include the psychotic state, delusions, and disorganized speech (Sullivan, Clarke, & Berg, 2015). However, adverse motor effects are seen with first-generation antipsychotics including tardive dyskinesia, akathisia, and dystonia (Sullivan et al., 2015). Subsequently, second-generation or atypical antipsychotics (AAP) were developed in the 1980s and are currently the treatment of preference (Sullivan et al., 2015). The mechanism of action for AAPs consists of targeting dopaminergic receptors and serotonergic receptors, and this combination of targeted receptors is thought to reduce the risk of side effects (Sullivan et al., 2015).

More recently, antipsychotics targeting serotonergic receptors, specifically 5-HT_{2A} receptors, are being developed for schizophrenia treatment and continue to show promise (Kantrowitz, 2020). Pimavanserin and Volinanserin are two such atypical

antipsychotics that are highly selective towards the 5-HT_{2A} receptor. Pimavanserin was approved by the FDA in 2016 for the treatment of hallucination and delusion associated with Parkinson's disease (Kantrowitz, 2020). Currently, Pimavanserin is in several clinical trials and interventional studies for schizophrenia treatment. However, Pimavanserin is not FDA approved for use in patients with schizophrenia.

Volinanserin is another promising therapy, since it is highly selective to 5-HT_{2A} receptor antagonists and is involved in animal models and active research for potential treatment as an atypical antipsychotic (Marques et al., 2020). However, Volinanserin is in preliminary stages as compared to Pimavanserin and is currently not FDA-approved for treatment. Volinanserin was developed and tested as an antipsychotic targeting only positive symptoms, but further research for FDA approval was discontinued.

Purpose of Study

In the current study, we perform a systematic review and meta-analysis to evaluate the efficacy of Volinanserin (MDL-100907) and Pimavanserin (ACP-103) in the treatment of schizophrenia. A literature search was performed by using PubMed, ClinicalTrials.gov, and Cochrane Database. Our search strategy consisted of the following strings: Pimavanserin or ACP-103 and Volinanserin or MDL-100907 and Schizophrenia or Schizophrenia spectrum. The purpose of this study is to analyze data available for Pimavanserin and Volinanserin as a treatment for schizophrenia. The effectiveness will be evaluated by conducting a meta-analysis of research available on these drugs (i.e., Pimavanserin and Volinanserin) in schizophrenia treatment, focusing on various measurements used to assess schizophrenia symptoms (i.e., PANSS, SGI, KSS, DAI-10).

CHAPTER II:

WHAT IS SCHIZOPHRENIA?

Schizophrenia is more recently classified as Schizophrenia Spectrum and other Psychiatric Disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Schizophrenia is a serious mental illness that is characterized by abnormalities in the form of delusions, hallucinations, disorganized thinking, or speech, grossly disorganized or abnormal motor behavior, and negative symptoms (Ritsner, Mar, Arbitman, & Grinshpoon, 2013). Historically, the symptoms of schizophrenia have been divided into positive and negative symptoms. Positive symptoms are the active manifestation of psychotic behavior, including delusions, hallucinations, and disorganized thinking/speech. The negative symptoms are less prominent, including diminished emotional expression and avolition (Ritsner et al., 2013) (Kahn et al., 2015). The development of psychotic features typically emerges between the late teens and mid-30s and is usually diagnosed before age 25 (Ritsner et al., 2013 (Schrimpf, Aggarwal, & Lauriello, 2018).

Schizophrenia is highly prevalent among homeless people, representing a maximum of 60% in some countries (Ayano, Tesfaw, & Shumet, 2019). Suicidal behavior has been seen in 5% to 6% of patients with schizophrenia. Such behavior is in response to command hallucinations, part of the positive symptoms or psychotic state (Ritsner et al., 2013). As part of the global burden of disease (GBD), recent innovations in statistical modeling have allowed for the derivation of detailed and geographically comparable epidemiological estimates for schizophrenia (Charlson et al., 2018). The burden of schizophrenia is increasing globally. One of the major factors is the lack of effective treatment (Charlson et al., 2018). In a study of global epidemiology by Charlson et al. 2018, cases rose from 13.1 (95% UI: 11.6–14.8) million in 1990 to 20.9 (95% UI:

18.5–23.4) million cases in 2016 (Charlson et al., 2018). The same study found that only 13.5% of people with schizophrenia met the clinical and social recovery criteria, suggesting that the outcome of schizophrenia treatment is not successful (Charlson et al., 2018).

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was published by the American Psychiatric Association (APA) and is the current tool for the diagnosis of schizophrenia (Ritsner et al., 2013). The definition of schizophrenia has evolved through the five editions of the DSM (I-V) editions. However, three major categories of symptoms are reflected in all editions: avolition or lack of initiating tasks, dissociation, and reality distortion (Ritsner et al., 2013; Tandon et al., 2013). In the fourth edition of the DSM, published in 1994, the diagnosis of schizophrenia had several subtypes that varied in symptom intensity. Over the two decades between the DSM-4 and DSM -5, the research found no benefits for the treatment of targeted schizophrenia subtypes, and the heterogeneity was poorly reflected by treatment (Reddy, 2014) (Tandon et al., 2013). Consequently, one major change in DSM-5 was the elimination of subtypes in schizophrenia diagnoses and a shift to diagnose schizophrenia as a spectrum disorder (Reddy, 2014) (Tandon et al., 2013).

DSM-5 has one chapter dedicated to the diagnosis of Schizophrenia Spectrum Disorder and other psychotic disorders. The schizophrenia spectrum is defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms (Ritsner et al., 2013). To be diagnosed with schizophrenia spectrum disorder, two or more symptoms should be present for a month, and one of these symptoms must be either 1, 2, or 3 from the summary of criterion A (See Table 1).

Table 1.

Summary of Criterion A for Schizophrenia Spectrum Disorder from the DSM-5

Symptoms (5 domains)	Key features
1. **Delusions**	fixed beliefs that are not amenable to change
2. **Hallucinations**	perception-like experiences that occur without external stimulus
3. **Disorganized thinking**	typically inferred from the individual disorganized speech
4. **Grossly disorganized or catatonic behavior**	manifests in a variety of ways from childlike silliness to unpredictable agitation. Catatonic behavior is a marked decrease in reactivity to the environment
5. **Negative symptoms**	diminished emotional expression or avolition

Two or more of the following symptoms/domains should be present for at least one month and one of the two symptoms should be delusions, hallucinations, or disorganized thinking.

Table 2.

Summary of diagnostic criteria for Schizophrenia Spectrum Disorder (Source: DSM-5)

Diagnostic Criteria	
Criterion A	Characteristic symptoms
Criterion B	Impairment in one or more major areas (work, interpersonal, self-care)
Criterion C	Continuous signs of disturbance must persist for a continuous period of at least 6 months. These 6 month includes 1 month that meets criteria A.
Criterion D	Schizoaffective disorder, depression, or bipolar disorder with psychotic features have been ruled out.
Criterion E	Disturbance is not attributable to physiological effects, drugs, or medication.
Criterion F	If there is a history of autism or communication disorder, at least 1 month of prominent hallucinations or delusions should be present.

The diagnostic criteria start with characteristic symptoms (criteria A) and are detailed in table one. These are the primary symptoms/domains of schizophrenia. After

confirming (criterion A) primary symptomology, criterion B-D is assessed (Table 2). All criteria and special cases that need more assessment to confirm the diagnosis are summarized in table two. Criterion *B-D* (Table 2) emphasizes symptomatology duration, other disorders, and drug effects that can be ruled out in the diagnosis.

Schizophrenia is conceptualized as a psychotic disorder, and this simply requires psychotic pathology, the core positive symptoms in the diagnosis. This includes delusions, hallucinations, and disorganized speech (Tandon et al., 2013). Negative symptoms can be described as decreased ability to experience pleasure from positive stimuli, lack of interest in social interactions, diminished emotional expression, and avolition. Avolition is a decrease in motivated, self-initiated, purposeful activities (Ritsner et al., 2013). A schizophrenia diagnosis requires the presence of delusion or hallucination in the absence of mood episodes.

In addition to the five symptom domains (Table 1), it is important to assess cognition, depression, and mania, associated features supporting diagnosis included in criteria B-D (Table 2*)*. Cognitive deficit is one aspect of the pathology that has been largely researched since is common and strongly linked to functional impairments. Cognitive deficits consist of a decrease in declarative memory, working memory, language function, executive control, and slow processing (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Cognitive impairments may persist when other symptoms are in remission and contribute to the disability from the disease(Ayano et al., 2019).

CHAPTER III:

SCHIZOPHRENIA TREATMENT

First-Generation Antipsychotics

The first FDA-approved drugs for the treatment of schizophrenia are typical or first-generation antipsychotics. These drugs target dopamine receptors to diminish positive symptoms that consist of altered perceptions, also referred to as a psychotic state (Hunter, Anderson, & Cox, 2015). Typical antipsychotics are dopamine antagonists, that is, drugs that bind to dopamine receptors but do not elicit a cellular response (Salahudeen & Nishtala, 2017). Typical antipsychotics are characterized by a high affinity for the D_2 dopamine receptor (Abbas & Roth, 2008). D_2 receptor blockade in the brain is a general pharmacodynamic property of all antipsychotics. More than 80% dopamine receptor blockade is associated with extrapyramidal symptoms, which are common drug-induced motor side effects (Horacek et al., 2006) (Krogmann et al., 2019). These adverse motor effects are frequently seen with first-generation antipsychotics. Such symptoms include tardive dyskinesia, acute dyskinesia, akinesia, and dystonia (Sullivan, 2015). The mechanism of action of these drugs has a narrow therapeutic window. That is, the margin between the therapeutic effectiveness and side effects is narrow, indicating that a higher dosage could lead to increased side effects (Sykes et al., 2017).

Second-Generation Atypical Antipsychotics

Second-generation or atypical antipsychotics (AAP) were developed around 1980 and are currently the preferred treatment for schizophrenia (Sullivan, 2015). AAPs have differences in their pharmacodynamic properties, including high selectivity for serotonin 5-HT_{2A}, dopamine (D2), and other systems (histaminergic, muscarinic, adrenergic) receptor activity (Horacek et al., 2006). The selectivity of the D2 receptor is the baseline

property for an antipsychotic effect. However, 2nd generation antipsychotics have a lower striatal D2 receptor occupancy and lower affinity. This explains the clinical characteristics of diminishing the negative side effects seen in first-generation antipsychotics(Sullivan et al., 2015) (Horacek et al., 2006).

5-HT2A Receptors

One of the theories of therapeutic efficacy in atypical antipsychotics is the high affinity for the 5-HT_{2A} receptor (Sullivan et al., 2015). Affinity is the firmness with which the drug binds to the receptor and is measured by the dissociation constant (*Kd*) value (Kantrowitz, 2020; Salahudeen & Nishtala, 2017). The commonly prescribed atypical antipsychotics can range from low/no affinity to high affinity towards the 5-HT_{2A} receptor.

There are fourteen known types of serotonin receptors, with 5-HT_{2A} as one of the most studied (Nichols, 2018). The serotonin 5-HT_{2A} receptor is important in the regulation of cortical functions and cognition and is also a target for inducing hallucinations by psychedelic drugs (Nichols, 2018). Abnormal 5-HT_{2A} receptor activity is associated with several psychiatric disorders, including depression, schizophrenia, and drug addiction (Duan, Zhang, Zhang, Wang, & Lei, 2015). The 5-HT_{2A} is expressed on the dendrites of glutamatergic neurons and GABAergic interneurons throughout the cortex, particularly in layer V (Pazos, Probst, & Palacios, 1987). In addition, intermediate 5-HT_{2A} expression is found in the hypothalamus, striatum, nucleus accumbens, amygdala, and hippocampus. This receptor regulates both glutamatergic and dopaminergic transmission.

Drugs with a High Affinity for 5-HT_{2A}

Currently, there is no Food and Drug Administration (FDA) approved non-dopaminergic antipsychotic as the primary treatment of schizophrenia (Kantrowitz,

2020). The 5-HT_{2A} receptor could be a new target for the development of novel schizophrenia treatments (Kantrowitz, 2020). All current available first-generation and second-generation antipsychotic drugs have dopamine D_2 receptor occupancy as a key feature and have remained the standard treatment for schizophrenia (Krogmann et al., 2019). However, dopamine D_2 receptor occupancy has side effects resulting from long-term usage. Thus, 5-HT_{2A} receptor occupancy can represent a new target to treat schizophrenia with fewer side effects.

Pimavanserin and Volinanserin are drugs with a high affinity toward the 5-HT_{2A} receptor and no dopaminergic receptor affinity. The following systematic review focuses on these two drugs in the treatment of schizophrenia. This could represent a new treatment option for schizophrenia with minimum side effects. Pimavanserin has been FDA approved for the treatment of hallucination and delusion associated with Parkinson's disease psychosis (Kantrowitz, 2020). Pimavanserin is an inverse agonist at the 5-HT_{2A} receptor. This means that it prevents any activity of the receptor, as opposed to blocking transmitter access to the receptor. It even blocks the intrinsic or constitutive activity of the receptor, even when no substance has bound to its binding site. An inverse agonist is a molecule that binds to the same receptor site as an agonist and exerts the opposite pharmacological response to that of a normal agonist (Salahudeen & Nishtala, 2017). Pimavanserin has no appreciable affinity for dopaminergic receptors, eliminating the possible side effects that are seen in atypical antipsychotics. Several clinical trials are currently active for adding Pimavanserin as an adjunctive treatment in schizophrenia treatment.

Volinanserin, is also an inverse agonist, of 5-HT_{2A} receptors. Volinanserin has been used in several animal studies to evaluate cellular mechanisms for therapeutic actions (Jones, Strassnig, & Harvey, 2020). Volinanserin is a promising therapy, since is

highly selective to the 5-HT_{2A} receptor and is involved in animal models and active research for potential atypical antipsychotic effects (Marques et al., 2020). However, Volinanserin is in preliminary stages as compared to pimavanserin and is currently not FDA approved for treatment. Volinanserin was developed and tested as an antipsychotic, targeting only positive symptoms. However, volinanserin is no longer the subject of further research for FDA approval. ACP-103 is the development name for Pimavanserin and MDL 100907 is the developmental name for Volinanserin (*Figure 1*). The 2D chemical structures of Pimavanserin and Volinanserin are shown in Figure 1.

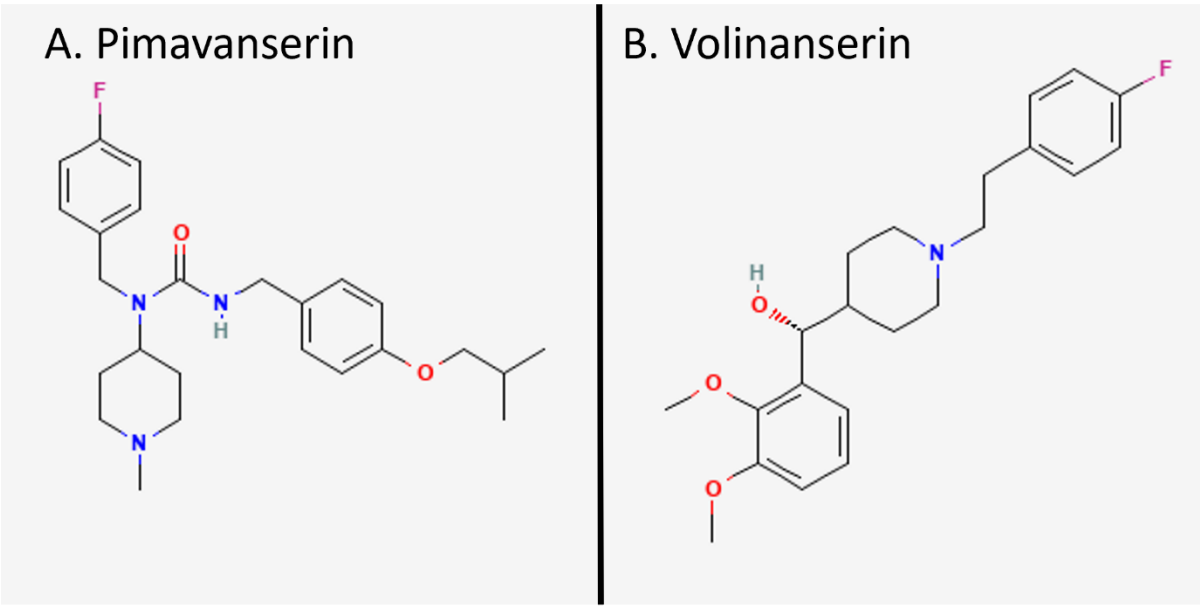

Figure 1.

2D chemical structure of Pimavanserin (ACP-103) and Volinanserin (MDL 100907)

Source: National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 5311271, Volinanserin. Retrieved February 14, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/Volinanserin.

CHAPTER IV:

ESTABLISHING PARAMETERS FOR SYSTEMATIC REVIEW

A first screening (preliminary search) was performed to establish parameters for systematic review. This step is in addition to the requirements established by PICO/PRISMA guidelines to perform a systematic review. In the current study, it was necessary to add this step, as it helped focus our research question. Our first search was conducted using the database PubMed. Literature search keywords included the following: atypical antipsychotic (AAP) or second-generation antipsychotics and 5-HT_{2A} and schizophrenia or schizophrenia spectrum. Literature search keywords are essential to target the pharmacological background of AAPs involving the 5-HT_{2A} receptor in schizophrenia treatment. Covidence.org was used to manage screenings and reviews in the PubMed database to collect and organize available studies with target keywords.

The first screening resulted in 308 published articles (Figure 2). Abstract and titles were evaluated based on the population of interest (schizophrenia), atypical antipsychotics (treatment), and pharmacology background (the 5-HT_{2A} receptor). The first screening identified 156 irrelevant articles for the study, leaving 152 studies for review. The second screening was then a full-text review of the remaining 152 publications. In the process of full-text review, we found 152 publications with different atypical antipsychotics and differences in the mechanism of action. Table three shows the names of atypical antipsychotics, mechanism of action, and affinity towards 5-HT_{2A} (see Table 3). The inclusion criteria were based on intervention (Atypical antipsychotic) for schizophrenia treatment and mentioning 5-HT_2 receptor mechanisms. The data collected was not comparable, since we found 15 distinct types of atypical antipsychotics, different study designs, and varying interventions. The affinity towards the receptor of interest (5-HT_{2A}) was variable (high to low affinity) (Table 3), and the mechanism of atypical

antipsychotics (antagonist & inverse agonist) were dissimilar. Based on the results shown in the Prisma flow diagram (Figure 2) and atypical antipsychotics (Table 3), we decided to proceed with a detailed search, for specific atypical antipsychotics, to have comparable data for the meta-analysis.

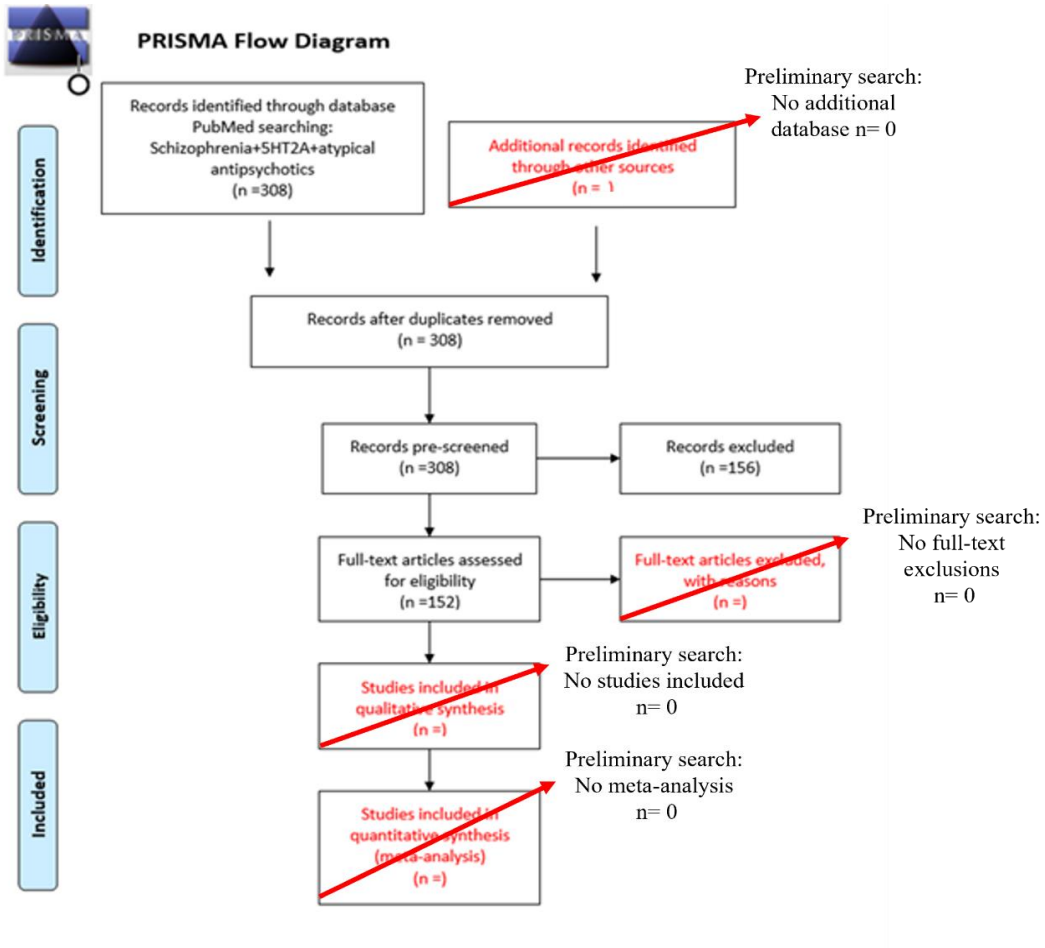

Figure 2.

Prisma Flow Diagram of initial search.
Identification of literature using database PubMed (n=308). No other source or database was used for the initial search. The screening included the elimination of duplicates (n=0), Records excluded, and not meeting inclusion criteria (n=156). Full-text articles were assessed for eligibility (n=152), no full-text articles are excluded since this search was preliminary (title and abstract). No studies were selected for qualitative/quantitative synthesis since the data was not comparable.

Table 3.

Atypical Antipsychotics found under the initial search

Atypical Antipsychotics	Mechanism of action	5-HT_{2A} Ki Values (nM)
Clozapine	antagonist	4
Pimavanserin	antagonist/inverse agonist	0.087nM
Risperidone	antagonist	0.2nM
Lurasidone	antagonist	2.03
Blonanserin	antagonist	0.812
Olanzapine	antagonist	4
Ziprasidone	antagonist	4.8
Iloperidone	antagonist	5.6
Perospirone	antagonist	1.3
Aripiprazole	partial antagonist	8.7
Brexpiprazole	antagonist	0.47
Quetiapine fumarate	antagonist	640
Asenapine	antagonist	0.06
Cariprazine	antagonist/partial agonism	18.8
Volinanserin	antagonist	0.36

Note: List of atypical antipsychotics found under initial search in full-text review with (ki) binding affinity constant and mechanism of action towards 5-HT_{2A}. Ki values are inversely proportional, high values suggest low affinity and low values suggest high affinity towards 5-HT_{2A} receptors.

Systematic Review: Pimavanserin OR ACP-103, Volinanserin OR M100907 AND schizophrenia OR schizophrenia spectrum.

Based on the preliminary search (Figure 2 & Table 3), parameters were adjusted to be more specific and included only drugs with a high affinity toward the 5-HT_{2A} receptor and not dopaminergic receptors. All atypical antipsychotics found in the preliminary search are included in Table 3. The Ki values in the table are inversely proportional, in that high values suggest low affinity and low values suggest high affinity towards the 5-HT_{2A} receptor. Asenapine (Ki 0.06) and risperidone ki 0.2nM (Table 3) have a high affinity toward 5-$HT_{2A.}$ However, they also target dopaminergic receptors. In this study, we want to focus on atypical antipsychotics with no direct dopaminergic

activity and high affinity to 5-HT_{2A}. Therefore, those drugs were excluded. Pimavanserin (0.087nM) and Volinanserin (0.36nM) both have a high affinity toward the 5-HT_{2A} receptor (Table 3) with no dopaminergic activity. The mechanism of action of both drugs is comparable since Pimavanserin and Volinanserin are inverse agonists towards the same receptor of interest.

Moving forward, our systematic review will consist of assessing the efficacy of Pimavanserin and Volinanserin in the treatment of schizophrenia. The process of the systematic review is to collect all data available on Pimavanserin and Volinanserin used for schizophrenia treatment. A meta-analysis will be conducted after the systematic review (Figure 3) with selected studies that meet the inclusion criteria (Ahn & Kang, 2018).

CHAPTER V:

SYSTEMATIC REVIEW

In the current study, we perform a systematic review and meta-analysis to assess the effectiveness of Volinanserin (MDL-100907) and Pimavanserin (ACP-103) in the treatment of schizophrenia. A systematic review was conducted following PRISMA and PICO guidelines. Prisma guidelines consist of a 27-item checklist addressing report requirements and a flow diagram that maps the number of records identified in the literature search and specifies studies included or excluded. Covidence.org software was used to manage and organize literature in this systematic review. Endnote was used as the reference manager to import literature search from the database to Covidence.org. A literature search was performed by using PubMed, ClinicalTrials.gov, and Cochrane database. Our search strategy consisted of the following strings: Pimavanserin or ACP-103 and Volinanserin or MDL-100907 and Schizophrenia or Schizophrenia spectrum. ACP-103 or M100907 are developmental code names for Pimavanserin or Volinanserin. The purpose of this study is to analyze data available for Pimavanserin and Volinanserin targeting schizophrenia illness. The effectiveness will be evaluated by conducting a meta-analysis on clinical trials available for these drugs for schizophrenia treatment.

Selection Criteria (Inclusion and Exclusion Criteria)

References of all articles that met the revised search criteria were imported from relevant databases (PubMed, ClinicalTrials.gov, Cochrane.org) to Covidence.org and Endnote and screened further. The first screening was based on the title and abstract. A total of 164 studies were found with the target keyword search terms (Pimavanserin and Volinanserin and Schizophrenia). Duplicates were removed and N=113 passed to the first screening. Irrelevant studies (N=73) were any studies that included the search terms but did not have enough data or information to measure the efficacy of schizophrenia

treatment. The remaining 40 studies were assessed for eligibility in a full-text review. The second screening was focused on meeting the required study design (experimental interventional studies phases (I-IV), patient population (schizophrenia), and intervention (Pimavanserin or Volinanserin).

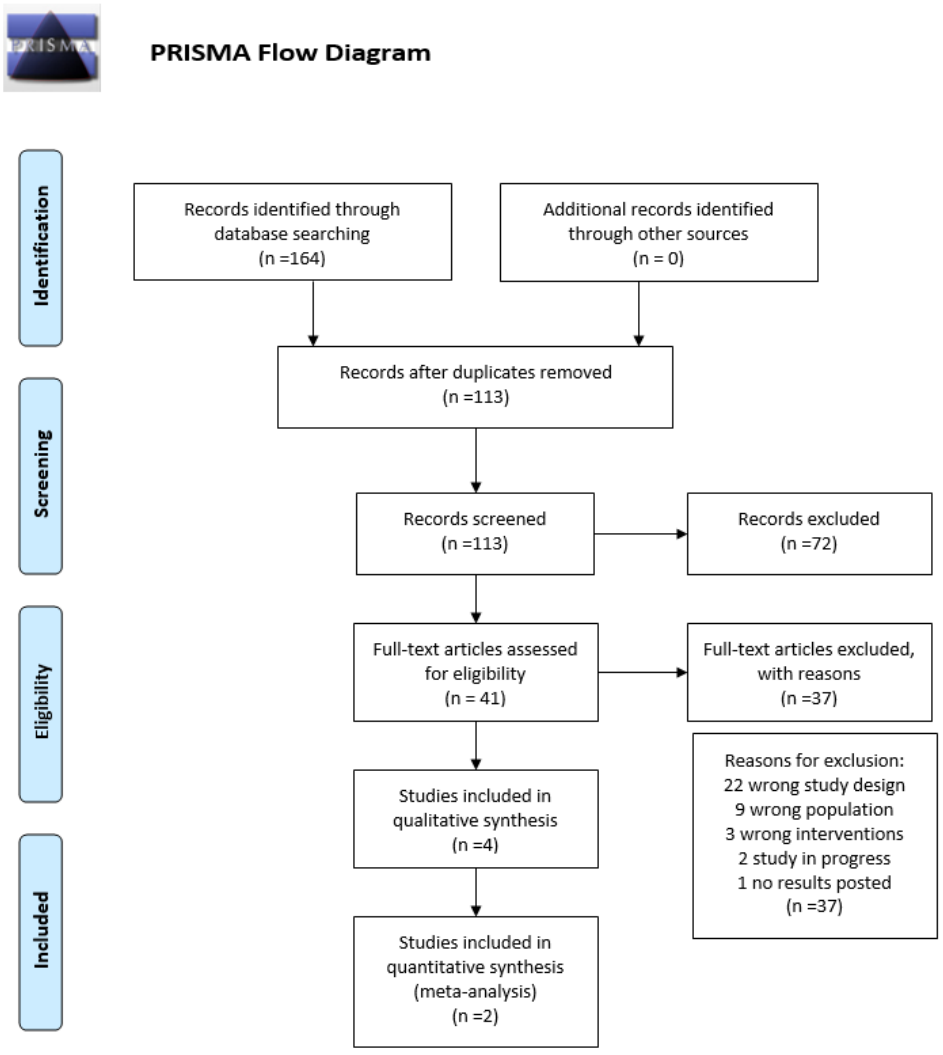

Figure 3.

Systematic Review Prisma Flow Diagram.
Identification of literature using database PubMed, Cochrane, and clinicaltrials.gov (n=164). The screening included the elimination of duplicates (n=51), Records excluded, and not meeting inclusion criteria (n=72). Full-text articles assessed for eligibility (n=41). Studies included in systematic review n=4, Meta-analysis n=2.

Second Screening -Full-Text Review (Table 4)

The full text of articles identified in the first screening stage (abstract and title) were reviewed to verify eligibility based on inclusion and exclusion criteria (Table 4). In this study, we focused on clinical studies that were classified as experimental interventional studies phases (I-IV) (Süt, 2014). These studies compare the effect of experimental treatment with appropriate control treatment on schizophrenia. Phase I studies are conducted on a small number of people to determine the safety of drugs or treatments. Phase II studies are conducted in a target population (e.g., schizophrenia spectrum) to determine the treatment effect. Phase III studies are conducted on a large sample of patients to determine whether the drug is better than the standard drug in efficacy and adverse effects. Clinical trials Phase IV studies are surveillance that is conducted on a drug that has been approved (Süt, 2014).

The following inclusion criteria were used for study selection in the full-text review: 1) Study design- experimental studies (interventional) Phase I-IV; 2) Patient population- Schizophrenia spectrum; and 3) Intervention-Volinanserin and/or Pimavanserin.

Studies that did not meet this inclusion criterion were excluded. The Prisma flow diagram (Figure 3) shows each step of selection and justification for studies that did not meet inclusion criteria and were excluded. A total of 164 studies were found with keyword search terms (Pimavanserin or ACP-103 and Volinanserin or MDL-100907 and Schizophrenia or Schizophrenia spectrum). Duplicates (N=51) were removed and a total of 113 studies passed to the first screening. After the first screening, 72 studies were classified as irrelevant (N=72). The remaining 41 studies were assessed for eligibility in the full-text review. A total of 37 studies were excluded for the following reasons: 22 wrong study designs, 9 wrong patient populations, 3 wrong interventions, 2 studies in progress, and 1 study with no results posted. A total of 4 studies were included in the

final systemic review. All 4 studies were for Pimavanserin, and no human studies or clinical trials on Volinanserin were identified.

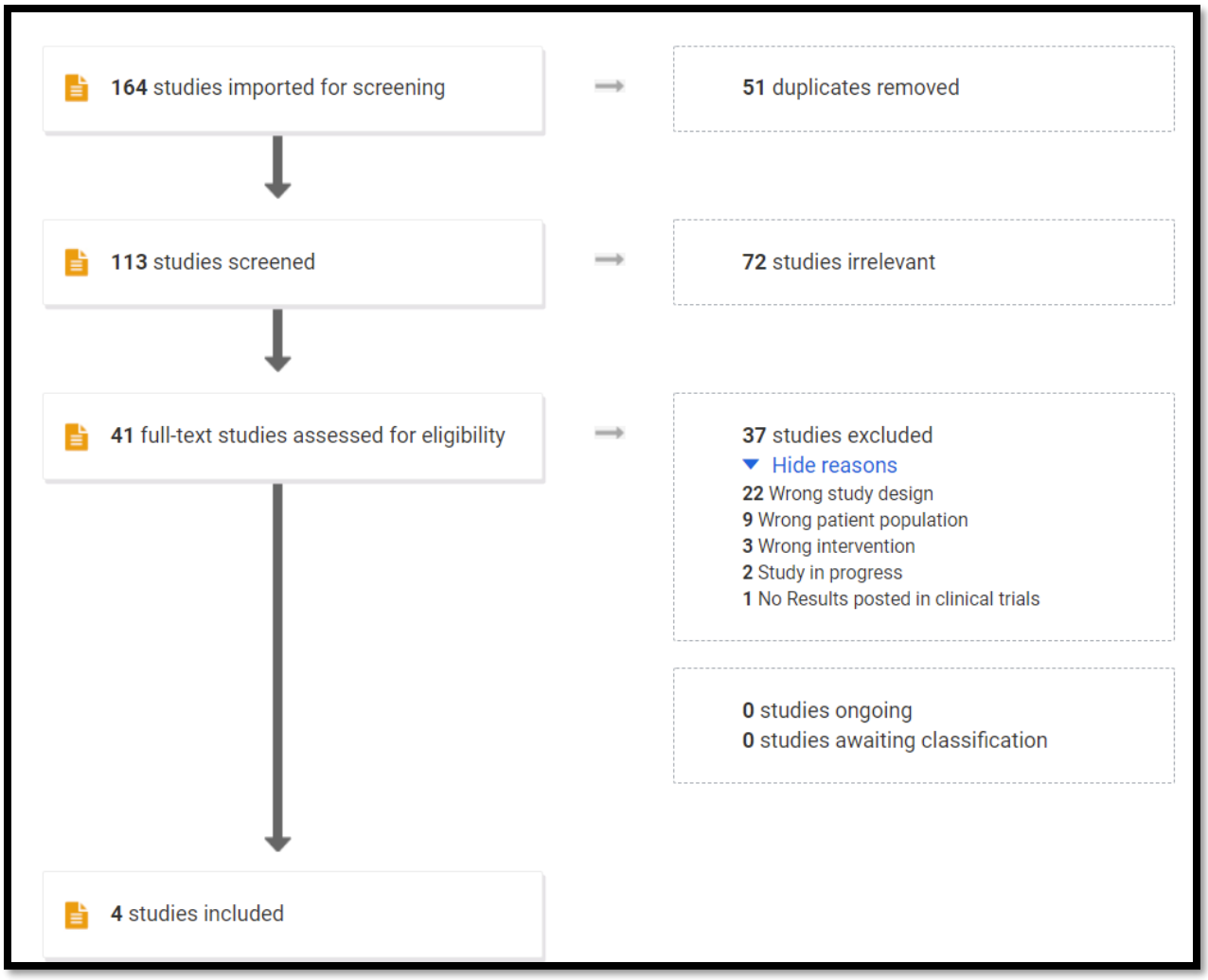

Figure 4.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) by Covidence.org.

Table 4.

Second screening -Full-Text studies assessed for eligibility, ACP-103 or M100907 are developmental code names for Pimavanserin or Volinanserin.

Reference	Source	Intervention	Condition or disease
(Davis, Zamora, Horowitz, & Leucht, 2021)	PubMed	Pimavanserin	Psychiatric disorders
(NCT00361166, 2006)	ClinicalTrial.gov	ACP-103	Motor effects
(NCT0087542, 2004)	ClinicalTrial.gov	ACP-103	Hallucinations Psychosis
(NCT01174004, 2010)	ClinicalTrial.gov	Pimavanserin	Parkinson /Psychosis
(NCT00658567, 2008)	ClinicalTrial.gov	Pimavanserin	Parkinson /Psychosis
(Meltzer, Massey, & Horiguchi, 2012)	PubMed	Serotonin receptors	Schizophrenia
(Meltzer, 2012)	PubMed	Pimavanserin	Psychosis
(Marek, 2015)	PubMed	Antipsychotics	Psychosis
(Krogmann et al., 2019)	PubMed	Antipsychotics	Schizophrenia
(Kantrowitz, 2020)	PubMed	Serotonin receptors	Schizophrenia
(Hunter et al., 2015)	PubMed	Pimavanserin	Psychiatric disorders
(Howland, 2016)	PubMed	Pimavanserin	Psychosis
(Hacksell, Burstein, McFarland, Mills, & Williams, 2014)	PubMed	Pimavanserin	Parkinson /Psychosis
(Gardell et al., 2007)	PubMed	ACP-103	Psychosis
(Garay et al., 2016)	PubMed	Serotonin receptors	Schizophrenia
(Friedman, 2018)	PubMed	Pimavanserin	Parkinson /Psychosis
(Friedman, 2017)	PubMed	Pimavanserin	Motor effects
(Diez-Alarcia et al., 2019)	PubMed	GPCR	Psychiatric disorders
(Baltzersen et al., 2020)	PubMed	Pimavanserin	Schizophrenia
(Abbas & Roth, 2008)	PubMed	Pimavanserin	Neuropsychiatric disorders
(NCT04531982, 2020)	ClinicalTrial.gov	Pimavanserin	Schizophrenia
(Euctr, 2019)	PubMed	Pimavanserin	Schizophrenia
(NCT03325556, 2017)	ClinicalTrial.gov	Pimavanserin	Dementia /Psychosis
(NCT02970305, 2016)	ClinicalTrial.gov	Pimavanserin	Schizophrenia
(NCT02970292, 2016)	ClinicalTrial.gov	Pimavanserin	Schizophrenia
(NCT02035553, 2010)	ClinicalTrial.gov	Pimavanserin	Schizophrenia
(Jones et al., 2020)	PubMed	Antipsychotics	Schizophrenia
(Ito, Nyberg, Halldin, Lundkvist, & Farde, 1998)	PubMed	MDL 100907	Schizophrenia
(Talvik-Lotfi et al., 2000)	PubMed	MDL 100907	Schizophrenia

Continue			
(de Paulis, 2001)	PubMed	MD100907	Psychiatric disorders
(Rauser, Savage, Meltzer, & Roth, 2001)	PubMed	Antipsychotics	Psychiatric disorders
(Ebdrup, Rasmussen, Arnt, & Glenthøj, 2011)	PubMed	Antipsychotics	Schizophrenia
(Carlsson et al., 1999)	PubMed	M100907	Psychiatric disorders
(Andrée et al., 1998)	PubMed	M100907	Psychiatric disorders
(Nasrallah, Fedora, & Morton, 2019)	PubMed	Pimavanserin	Hallucinations Psychosis
(Meltzer & Roth, 2013)	PubMed	Pimavanserin	Psychiatric disorders
(Meltzer et al., 2010)	PubMed	Pimavanserin	Parkinson /Psychosis
(Offord, Wong, & Nyberg, 1999)	PubMed	M100907	Psychiatric disorders
(Nilsson, Markinhuhta, & Carlsson, 2006)	PubMed	Antipsychotics	Psychiatric disorders
(Zimering & Nadkarni, 2019)	PubMed	5-Hydroxy tryptamine	Schizophrenia
(Yadav, Kroeze, Farrell, & Roth, 2011)	PubMed	Serotonin receptors	Psychiatric disorders

Table 5.

Studies included in the systematic review (Figure 3).

Study /Year	Title	Type of Study	Intervention	N	Age range	Sex	Comments
Nasrallah et al. 2019	Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with Pimavanserin, a serotonin 5HT-2A receptor inverse agonist	Retrospective Study	Pimavanserin	10	21-77	5F 5M	none
Meltzer et al. 2012	Pimavanserin, selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance the efficacy of haloperidol, 2mg/day: comparison with reference dose risperidone, 6mg/day.	Randomize double-blind clinical study	Risperidone, Haloperidol, Pimavanserin	423	18-65	ND	This study is divided into 4 groups. Each group with a different intervention
NCT02970305 2016	Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE)	Clinical Study	Pimavanserin, Placebo	403	18-55	135 F 33.5% 268 M 66.5%	12 outcome measures
NCT02970292 2016	Efficacy and Safety of Adjunctive Pimavanserin for the Treatment of Schizophrenia (ENHANCE-1)	Clinical Study	Pimavanserin, Placebo	396	18-55	150 F 37.9% 246 M 62.1%	8 outcome measures

Table 6.

Study NCT02970305

Study: NCT02970305	Pimavanserin (Mean)	SE	N	SD	Placebo (Mean)	SE	N	SD	Effect Size
Outcome 1 (NSA-16)	-10.5	0.69	199	9.73	-8.8	0.69	201	9.78	-0.17
Outcome 2 (PSP-Scale)	8.1	0.7	199	9.87	8.4	0.75	201	10.60	-0.03
Outcome 3 (NSA-16)	n/a	n/a	174	n/a	n/a	n/a	173	n/a	n/a
Outcome 4 NSA-16	-0.7	0.06	199	0.85	-0.7	0.06	201	0.85	0.00
Outcome 5 NSA-16	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Outcome 6 (CGI-SCH-S)	-0.6	0.06	199	0.85	-0.6	0.06	201	0.85	0.00
Outcome 7 (CGI-SCH-I)	3.1	0.07	174	0.92	3.1	0.06	173	0.79	0.00
Outcome 8 CGI-SCH-I	27%	n/a	n/a	n/a	23%	n/a	n/a	n/a	n/a
Outcome 9 (PANS)	-8.7	0.75	199	10.58	-8.6	0.76	201	10.7	-0.01
Outcome 10 (PANS)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Outcome 11 (BACS) Cognition	3.3	0.71	197	10.09	4.16	0.696	199	9.82	-0.08
Outcome 12 (DAI-10)	0.2	0.23	199	3.24	0.20	0.19	201	2.69	0.00
Outcome 13 (KSS) Sleepiness	-0.3	0.12	199	1.69	-0.6	0.13	201	1.84	0.17

Phase 2, Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Pimavanserin as an adjunctive treatment for the negative symptoms of schizophrenia. Data calculated based on study results (Mean, SE, N) from clinicaltrials.gov.NSA-16, 95% confidence interval -1.9(-3.8, -0.1). Outcomes three, five, and ten have subscale measurements. n/a (not applicable)

Table 7.

Study NCT02970292

Study: NCT02970292	Pimavanserin (Mean)	SE	N	SD	Placebo (Mean)	SE	N	SD	Effect Size
Outcome 1 (PANSS)	-15.3	0.93	173	12.23	-13.4	0.83	189	11.4	-0.16
Outcome 2 (CGI-S)	-0.8	0.06	173	0.79	-0.7	0.05	189	0.69	-0.14
Outcome 3 PANSS subscale score	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PANSS positive BL	23	0.25	193	3.47	22.8	0.23	196	3.22	0.06
CFBL to 6 W	-5.4	0.34	193	4.72	-4.9	0.3	196	4.20	-0.11
PANSS Negative Scale BL	23	0.29	193	4.03	23.1	0.29	196	4.06	-0.02
CFBL to 6 W	-2.8	0.28	193	3.89	-2.1	0.28	196	3.92	-0.18
PANSS general Psychopathology BL	42.4	0.45	193	6.25	42.2	0.45	196	6.30	0.03
CFBL to 6 W	-7.2	0.47	193	6.53	-6.4	0.47	196	6.58	-0.12
Outcome 4 PANSS 20-30% reduction	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
reduction of ≥20%	0.56	n/a	193	n/a	0.51	n/a	196	n/a	n/a
reduction of ≥30%	0.37	n/a	193	n/a	0.34	n/a	196	n/a	n/a
Outcome 5 (CGI-I)									
MN Response	68	n/a	193	n/a	65	n/a	196	n/a	n/a
OC Response	68	n/a	173	n/a	65	n/a	189	n/a	n/a
Outcome 6 (CGI-I)	2.8	0.07	173	0.92	3	0.07	189	0.96	-0.21
Outcome 7 (PSP)	6.8	0.71	173	9.34	5.7	0.64	188	8.78	0.12
Outcome 8 (DAI-10)	0.4	0.2	173	2.63	0.4	0.2	188	2.74	0.00
Outcome 9 (KSS)	-0.5	0.12	173	1.58	-0.2	0.12	189	1.65	-0.19

Phase 3. Randomized, Double-Blind, Placebo-Controlled Study to evaluate the efficacy and safety of adjunctive Pimavanserin for the treatment of schizophrenia. PANSS 95% confidence interval of primary outcome -2.1 (-4.5,0.4). n/a (not applicable)

CHAPTER VI:

SYSTEMATIC REVIEW-DISCUSSION

Nasrallah et al. 2019

Nasrallah et al. (2019) are one of the four studies that are included in the systematic review. This study consists of ten cases with refractory schizophrenia. Refractory psychosis is a classification used when dopamine D2 receptor antagonist atypical antipsychotics are not effective in treating the positive symptom of schizophrenia (Nasrallah et al., 2019). In this study, Pimavanserin is evaluated as an adjunctive treatment with clozapine.

Results of this study showed marked response to Pimavanserin at a dosage of 34 mg/day within four to eight weeks. The efficacy of Pimavanserin as adjunctive therapy with clozapine was evaluated in six cases with poor or partial response to clozapine (200-800mg/day). Within four to eight weeks of Pimavanserin (34mg/day) additional improvement was seen in positive and negative symptoms. Pimavanserin also was evaluated as monotherapy in four cases. For Case 1, auditory hallucinations disappear within 4 weeks. For Case 2, within two weeks auditory hallucinations stopped. For Case 3, auditory and visual hallucinations disappeared within 4 to 5 weeks. For Case 4, auditory and visual hallucinations disappeared after 2 months. These results have important implications for the management of the clinical subtypes of schizophrenia syndrome with refractory hallucination and delusions that are resistant to the traditional dopamine D_2 receptor antagonist (Nasrallah et al., 2019).

Nasrallah et al. (2019) were ultimately not used for the meta-analysis as it is a non-randomized, non-controlled clinical study on ten patients and is considered a retrospective study (clinical observation). This study doesn't follow study design inclusion criteria. However, the findings are important to note.

Meltzer et al. 2012

Meltzer et al. 2012 are also one of the four studies that are included in the systematic review (Figure 3). This randomized, multicenter, double-blind six-week trial (Table 5) was done to evaluate the effectiveness and safety of combining Pimavanserin with risperidone, and haloperidol to determine antipsychotic efficacy. Positive and Negative Syndrome Scale (PANSS) total score, as well as negative and general symptoms, had improvements with the combination of risperidone and Pimavanserin. However, the combination of Haloperidol and Pimavanserin was not significantly different compared with the placebo (Meltzer, Elkis, et al., 2012).

This study was not included in the meta-analysis because it combines Pimavanserin with risperidone and haloperidol (atypical antipsychotics) at a different dosage. This is a limiting factor to be evaluated in Meta-analysis since the other two clinical trials use Pimavanserin as adjunctive treatment compared with placebo, but atypical antipsychotic dosage and type are not compared or mentioned in the data. A statistical summary was performed with the same measurements (comparable outcomes) and interventions (Pimavanserin + unknown atypical antipsychotic compared with placebo + unknown atypical antipsychotics).

Study NCT02970305

This study is clinical trial NCT02970305 and evaluates the efficacy and safety of Pimavanserin as an adjunctive treatment for the negative symptoms of schizophrenia (Table 6). This study is a phase 2 randomized clinical trial with 403 participants. The intervention (drug) used is Pimavanserin with a dosage of 34mg, 20mg, or 10g tablets + background antipsychotic compared with the control (placebo) group (NCT02970305, 2016). A total of 12 outcomes measures were used to evaluate efficacy. All scales were measured based on change from baseline to week 26. Study NCT02970305 uses the

following scales: Negative Symptom Assessment-16 (NSA-16); Personal and Social Performance Scale (PSP); Proportion of Negative Symptom Assessment (NSA-16); Global Negative Symptoms; NSA-16 Domain score; Clinical Global Impression of Schizophrenia Scale-Severity of Negative Symptoms; Proportion of CGI-SCH-I responder; Positive and Negative Syndrome Scale total score (PANSS); PANSS subscale; Assessment of Cognition in Schizophrenia; Drug Attitude Inventory; and Karolinska Sleepiness Scale. Results of study NCT02970305 are shown in Table 6. The effect size on each outcome measure was calculated as shown in Table 6. These results are calculated based on results (Mean, N, SE) available on clinicaltrials.gov.

Study NCT02970292

This study is a clinical trial that evaluates the efficacy and Safety of Adjunctive Pimavanserin for the Treatment of Schizophrenia. This study is an interventional study, Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin for the Treatment of Schizophrenia. The Intervention in this study is Pimavanserin at a dosage of 34mg, 20mg, or 10mg + background antipsychotic compared with placebo(NCT02970292, 2016). A total of 8 outcomes measures are used to evaluate efficacy. All scales were measured based on change from baseline to week 6. The following scales were used: Positive and Negative Syndrome Scale (PANSS); Clinical Global Impression-Severity (CGI-S); PANSS Subscale Scores; PANSS Responders; Clinical Global Impression-Improvement (CGI-I); Clinical Global Impression-Improvement (CGI-I); Personal and Social Performance (PSP) Scale; Drug Attitude Inventory (DAI-10); and Karolinska Sleepiness Scale (KSS). Results of study NCT02970292 are shown in Table 7, and the effect size was calculated for each outcome for meta-analysis in Chapter VII. These results were calculated based on results (Mean, N, SE) available at clinicaltrials.gov.

CHAPTER VII:

META-ANALYSIS

After performing a systematic review, two studies met the inclusion criteria for statistical analysis (See Figure 4). These studies are randomized, double-blind, placebo-controlled clinical trials. They evaluate the efficacy and safety of Pimavanserin for the treatment of schizophrenia. Review Manager 5.4.1 software (RevMan 5, Version 5.4, The Cochrane Collaboration, 2020) was used to perform a summary statistic of Pimavanserin as an adjunctive treatment. The data is available at clinicaltrials.gov for studies: NCT02970305 and NCT02970292. To evaluate the efficacy of treatment, we compared the following outcomes: Positive and Negative Syndrome Scale (PANSS), clinical global impression of schizophrenia improvement (CGI-SCH-I), drug attitude inventory (DAI), and Karolinska sleepiness scale (KKS). The analysis method used for statistical analysis is inverse variance, random effect model, and the effect measure is by mean difference. The study confidence interval is 95%.

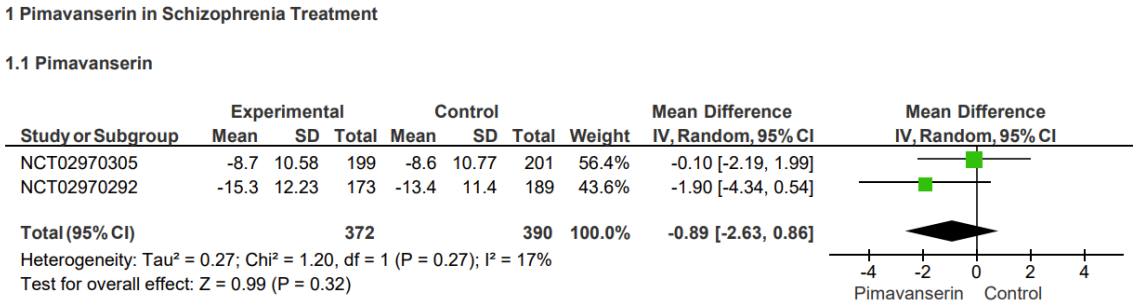

Figure 5.

Summary statistic for clinical trials evaluating Pimavanserin as an adjunctive treatment for schizophrenia. *The following analysis is based on the positive and negative syndrome scale (PANSS) used in both studies to assess schizophrenia psychopathology.*

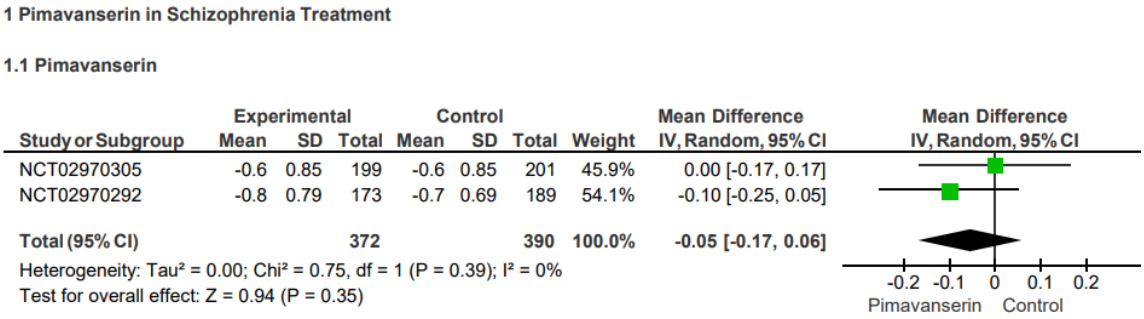

Figure 6.

Summary statistic for Clinical Global Impressions (CGI) scale in studies evaluating Pimavanserin as adjunctive treatment for schizophrenia.

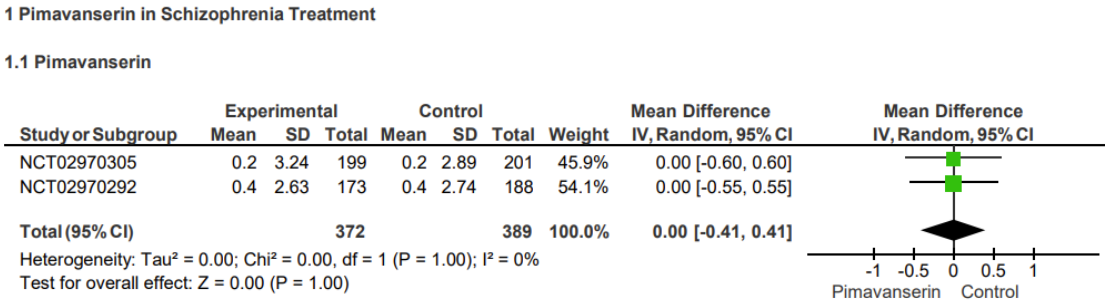

Figure 7.

Summary statistic for Drug Attitude Inventory (DAI-10) in studies evaluating Pimavanserin as adjunctive treatment for schizophrenia.

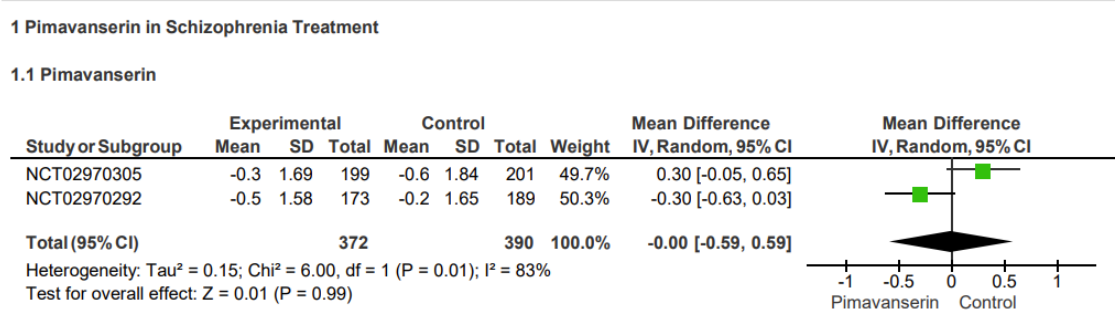

Figure 8.

Summary statistics for Karolinska Sleepiness Scale (KSS) in studies evaluating Pimavanserin as adjunctive treatment for schizophrenia.

Interpretation of Meta-Analysis Results

The positive and Negative Syndrome Scale (PANSS) is a 30-item clinician-rated instrument developed to assess both positive and negative symptoms of schizophrenia psychopathology. To perform the statistical summary, we used the total score change (end of study - baseline) of studies NCT02970305 and NCT02970292. Study NCT02970305 has more weight (56.4%), this value is proportional to the sample size (Figure 5). The pooled PANSS data is the overall effect seen in the statistical summary (Figure 5). An advantage for adjunctive pimavanserin of 0.99 SD with a p-value of 0.32. Thus, the pooled data from the two studies demonstrate a considerable, but not statistically significant, benefit of pimavanserin for PANSS outcomes.

The clinical Global Impressions of Schizophrenia – Severity Scale (CGI-SCH-S) is used to evaluate the patient's global functioning before and after the intervention. CGI-SCH scale measures the severity of psychopathology from 1(improve) to 7 (worse). We evaluate this scale in Figure 6. The pooled clinical global impression data is the overall effect seen in figure 6. Therefore, results indicate an advantage for adjunctive pimavanserin of 0.94 SD with a p-value of 0.35. Thus, the pooled data from the two studies demonstrate a considerable, but not statistically significant, benefit of pimavanserin for CGI-SCH-S outcome.

Drug attitude Inventory (DAI-10) contains 6 items to evaluate patients' attitudes towards medications. Positive total scores indicate adherence, and negative total scores indicate non-adherence. A statistical summary includes a comparison of both studies for the DAI-10 scale (figure 7). The pooled Data Attitude inventory showed no deviation from a neutral outcome, $Z = 0.00$ with a p-value of 1. Therefore, the pooled data from the two studies demonstrated no evidence for adjunctive pimavanserin producing a change in the drug attitude inventory scale.

Karolinska Sleepiness Scale (KSS) is a self-reported measure of a patient's level of drowsiness. The scoring scale ranges from 1 (extremely alert) to 9 (very sleepy). The scale's mean difference values are compared in Figure 8. The pooled data from KSS showed almost no deviation from a neutral outcome Z=0.01 with a p-value of 0.99. Therefore, the pooled data from the two studies demonstrated no evidence for adjunctive pimavanserin to produce a variation in KSS outcome.

CHAPTER VIII:

CONCLUSION, LIMITATIONS, AND FUTURE DIRECTIONS

Pimavanserin and Volinanserin are drugs with a high affinity toward the 5-HT_{2A} receptor and no dopaminergic receptor affinity. This is an advantage since atypical antipsychotics have several side effects caused by dopaminergic affinity. The 5-HT_{2A} receptor occupancy can represent a new target to treat schizophrenia with fewer side effects.

A systematic review was performed to evaluate the efficacy of Volinanserin and Pimavanserin in the treatment of schizophrenia. There are limited studies investigating the effectiveness of Volinanserin as a treatment for schizophrenia, all of which are in vitro and in vivo animal studies. That is, no research has investigated whether Volinanserin may be effective in the treatment of schizophrenia symptoms, resulting in no Volinanserin studies that met the inclusion criteria for the current systemic review. Pimavanserin has been FDA approved for the treatment of hallucination and delusion associated with Parkinson's disease psychosis (Kantrowitz, 2020). Pimavanserin was the subject of several interventional studies evaluating the safety and efficacy of schizophrenia treatment.

Nasrallah et. al, 2019 evaluate Pimavanserin as adjunctive therapy with clozapine. As result, several cases showed improvement in their positive symptoms (auditory/visual hallucinations). This is important for the management of the clinical subtypes of schizophrenia syndrome with refractory hallucination and delusions that are resistant to the traditional dopamine D2 receptor antagonist (Nasrallah et al., 2019). Another study by Meltzer et al. (2012) showed improvement in one combination of atypical antipsychotic (risperidone) and Pimavanserin but no significant effect with other combination (haloperidol and Pimavanserin).

Study NCT02970292 and NCT02970305 are clinical studies completed with their results available on clinicaltrials.gov. These studies have several outcome measurements (PANSS, CGI, DAI, and KSS) that are compared in this meta-analysis (Chapter VI). Study NCT02970305, no difference is seen with Pimavanserin as adjunctive treatment when comparing PANSS, CGI, and DAI. However, the pimavanserin group was slightly drowsier on the KSS scale. Study NCT02970292 favors Pimavanserin as adjunctive treatment on PANSS, CGI, and KSS scales. Based on the PANSS and SGI outcome measures there was a notable but non-significant trend towards increased efficacy of adjunctive pimavanserin. There is no overall trend in drug attitude and degree of drowsiness.

Limitations

There are various limitations to note. Study NCT02970305 and NCT02970292 evaluate Pimavanserin as adjunctive treatment with patients' main treatment of atypical antipsychotics. Studies NCT02970292 and NCT02970305 used identical dosages of Pimavanserin. However, they differ in study duration and primary treatment (standard antipsychotic). It is also important to consider the time frame difference in studies used for the meta-analysis since outcome values are based on change differences from baseline to end of the study. In study NCT02970305, the time frame and outcome values are based on changes seen from baseline to week 26. Study NCT02970292, consisted of six weeks of evaluation with outcomes measured from baseline to Week 6. This is an important factor to consider when evaluating outcomes since both studies have a different time frame. The systematic review and meta-analysis were also limited to the sparse literature available with key terms that include drugs of interest and target population.

Future Directions

Future studies should evaluate the synergistic effect and interactions caused by Pimavanserin when combining additional atypical antipsychotics. Since most atypical antipsychotics have already acted on the 5-HT_{2A} receptor, it would be particularly interesting to add them to first-generation antipsychotics Chlorpromazine and Haloperidol. Currently, however, clinical trials are running with several atypical antipsychotics used as primary treatment and Pimavanserin as adjunctive.

In closing, results suggest that the 5-HT_{2A} receptor is a key component for the treatment of schizophrenia. Study NCT02970292 and NCT02970305, are clinical studies completed and used in the meta-analysis (Chapter VI). Currently, patients are being recruited for extended studies of Pimavanserin to treat schizophrenia (clinicaltrials.gov). Pimavanserin is a promising and apparently safe approach when combined with atypical antipsychotics and is worthy of continued evaluation for schizophrenia treatment.

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