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Review of pharmacologic treatment in cluster A personality disorders

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Abstract

Introduction: A personality disorder is a pervasive and enduring pattern of behaviors that impacts an individual's social, occupational, and overall functioning. Specifically, the cluster A personality disorders include paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder. Patients with cluster A personality disorders tend to be isolative and avoid relationships. The quality of life may also be reduced in these individuals, which provokes the question of how to treat patients with these personality disorders. The purpose of this review is to evaluate the current literature for pharmacologic treatments for the cluster A personality disorders.

Methods: A Medline/PubMed and Ovid search was conducted to identify literature on the psychopharmacology of paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder. There were no exclusions in terms of time frame from article publication or country of publication, in order to provide a comprehensive analysis; however, only articles that contained information on the cluster A disorders were included.

Results: Minimal evidence regarding pharmacotherapy in paranoid and schizoid personality disorders was found. Literature was available for pharmacologic treatment of schizotypal personality disorder. Studies evaluating the use of olanzapine, risperidone, haloperidol, fluoxetine, and thiothixene did yield beneficial results; however, treatment with such agents should be considered on a case-by-case basis.

Discussion: Most of the literature analyzed in this review presented theoretical ideas of what may constitute the neurobiologic factors of personality and what treatments may address these aspects. Further research is needed to evaluate specific pharmacologic treatment in the cluster A personality disorders. At this time, treatment with pharmacologic agents is based on theory rather than evidence.

Keywords: schizotypal personality disorder, schizoid personality disorder, paranoid personality disorder, cluster A, pharmacotherapy

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Introduction

Personality disorders are said to exist when a person's pattern of perceiving, relating to, and thinking about the environment and oneself results in maladaptive behavior and significant impairment in interpersonal relationships and interactions. These patterns of inner experience and behavior are inflexible and pervasive, causing clinically

significant distress or impairment in social, occupational, or other important areas of functioning.[1]

Personality disorders are often characterized by symptoms (eg, psychoticism in schizotypal personality disorder) that are similar or nearly identical to pharmacotherapy-responsive symptoms seen in other mental disorders (eg, auditory hallucinations in schizophrenia). However, symptomatic similarity does not equal etiologic or pathophysiologic similarity; therefore, similarity in response and tolerability of pharmacotherapy cannot be assumed. It was this presumed difference in etiology between historically axis I (more biologic in origin) and axis II (more psychological in origin) disorders that contributed to previous recommendations discouraging the use of pharmacotherapy for personality disorders.[2]

However, for certain dimensions of personality, such as impulsive-aggression, schizotypy, and novelty seeking, neurobiologic correlates have been demonstrated, suggesting that some aspects of personality disorders may be amenable to pharmacologic intervention.[3-5] Based on these findings and the results of efficacy studies, recent guidelines now recommend the judicious use of pharmacotherapy as an adjunctive treatment in the overall management of patients with severe personality disorder.[6] There are currently no medications with US Food and Drug Administration approval for use in personality disorders. All use of medications for symptoms of personality disorders is considered off-label. This review will focus on available evidence regarding the use of pharmacotherapy for paranoid, schizoid, and schizotypal personality disorders, collectively known as the cluster A personality disorders.

Pharmacotherapy for personality disorders tends to be symptom specific, focusing on dimensions of personality believed most likely to be responsive to pharmacotherapy and that typically warrant the most clinical attention. These dimensions include affective dysregulation (eg, angry, anxious, depressed, labile mood), cognitive-perceptual symptoms (eg, auditory, visual hallucinations), and impulsive aggression (eg, self-cutting, suicidality).[2,6] The use of pharmacotherapy is adjunctive, with the goal of providing enough stabilization to make it easier or possible for the patient to engage in psychosocial interventions. The risks and benefits of pharmacotherapy must be carefully considered, especially in a situation where expected benefits may be modest.[2,6] It is the goal of this review to provide answers to questions regarding the use of pharmacotherapy for cluster A personality disorders and bring the reader up to date regarding what is known and unknown about the effectiveness of this practice.

Methods

A literature review on the psychopharmacology of paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder was conducted through PubMed and Ovid searches using combinations of the following search terms: *schizotypal personality disorder treatment*, *pharmacotherapy schizotypal*, *antipsychotic schizotypal*, *risperidone schizotypal*, *olanzapine schizotypal*, *aripiprazole schizotypal*, *quetiapine schizotypal*, *paliperidone schizotypal*, *clozapine schizotypal*, *ziprasidone schizotypal*, *lurasidone schizotypal*, *asenapine schizotypal*, *iloperidone schizotypal*, *haloperidol schizotypal*, *amitriptyline schizotypal*, *fluoxetine schizotypal*, *guanfacine schizotypal*, *pergolide schizotypal*, *schizoid personality disorder pharmacotherapy*, *pharmacotherapy of personality disorders*, *paranoid personality disorder*, and *cluster a personality disorders*. Only papers that contained information on the cluster A personality disorders were included. There were no exclusions in terms of time frame from article publication or country of publication, in order to provide a comprehensive analysis. Of note, many of the articles included were based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) diagnostic criteria. There were no changes made between DSM-IV and DSM-5 regarding the criteria for the personality disorders.

Paranoid Personality Disorder

Paranoid personality disorder is described as a pervasive suspicion of others' motives and behaviors in a variety of contexts. Individuals with this disorder may be considered "odd" or "eccentric" by others and have a lack of close relationships. The Table more thoroughly defines this disorder and diagnostic criteria per DSM-5. The prevalence of paranoid personality disorder is not exactly known, but is estimated to be between 2% and 4% of the population.[1] This review intends to summarize the literature regarding treatment for paranoid personality disorder, specifically pharmacotherapy.

Overall, a review of the literature yields very little research regarding pharmacotherapy options for the treatment of paranoid personality disorder. The reason for this has been theorized by multiple authors. The belief is that a paucity of research exists because of the general lack of trust patients with paranoid personality disorder have for others, with psychiatric providers being no exception.[7,8] In reference to paranoid personality disorder, Angstman and Rasmussen[7] wrote, "These patients are difficult to engage in a therapeutic relationship for medical or mental health issues... Physicians should expect belittling comments, accusations, and potentially litigious threats from these patients..." This behavior not only limits the likelihood of the patient seeking medical attention but

TABLE: ***Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, personality disorders definitions and diagnostic criteria**

Personality Disorder	Definition	Diagnostic Criteria
Paranoid	Pattern of distrust and suspicion such that others' intentions are interpreted as malignant	A. ≥4 of the following: (1) Questions if others are manipulating or deceiving him or her (2) Doubts the loyalty of friends and family (3) Believes that confiding in others will lead to manipulation of given information (4) Interprets hidden meanings in nonthreatening remarks (5) Bears grudges (6) Believes personal assaults are being taken against his or her repute (7) Distrusts the faithfulness of his or her significant other without justification B. Does not occur exclusively during the course of a psychotic disorder and is not attributable to a medical condition
Schizoid	Pattern of disengagement from social connections and a flattened range of emotional articulation	A. ≥4 of the following: (1) Avoids or dislikes close relationships (2) Prefers solitary activities (3) Has minimal interest in sexual interactions with other (4) Derives no enjoyment from activities (5) Has few close friends, excluding family (6) Apathetic to praise or criticism (7) Displays emotional aloofness or flattened affectivity B. Does not occur exclusively during the course of a psychotic disorder and is not attributable to a medical condition
Schizotypal	Pattern of severe discomfort in intimate relationships, mental or perceptual alterations, and peculiarity of behavior	A. ≥5 of the following: (1) Thoughts of reference (2) Strange beliefs or magical ideas (3) Perceptual alterations (4) Abnormal thinking and speech (5) Paranoia (6) Inappropriate or restricted affect (7) Atypical behaviors (8) Lack of close relationships, excluding family (9) Presence of social anxiety B. Does not occur exclusively during the course of a psychotic disorder and is not attributable to a medical condition

also detracts from the collaborative therapeutic relationship between provider and patient. Triebwasser et al[8] suggest that ambivalence in the diagnosis itself contributes to the lack of research. Because the predominant characteristic of paranoid personality disorder is paranoia itself—a common feature of numerous other psychiatric conditions, such as posttraumatic stress disorder and schizophrenia—clinicians may be more apt to give patients a diagnosis of a comorbid condition rather than the personality disorder. Overall, the characteristics of paranoid personality disorder (ie, bearing grudges) likely have contributed to the dearth of research into the treatment of this disorder.

Of the few articles written, a case series by Birkeland[9] retrospectively analyzed the psychiatric hospitalization course of 15 patients in Denmark with paranoid personality disorder. Clinical Global Impression was rated at first admission and the last psychiatric visit in order to assess any clinical improvement. Birkeland[9] found that a total of 7 patients received an antipsychotic; the most commonly prescribed one was flupentixol. Other antipsychotic medications prescribed included bromperidol and promazine. The median duration of treatment was 15 weeks. Of the 15 patients, only 4 who received antipsychotic medication therapy were present for the 6-week follow-up. All 4 of these patients demonstrated improvement as

measured by the Clinical Global Impression Improvement (CGI-I) scale (CGI-I mean 1.8 compared with baseline CGI Severity [CGI-S] mean 5.5), over those who did not receive antipsychotic medication (CGI-I mean 4.0 compared with baseline CGI-S mean 4.8). At the last follow-up visit, 3 of the 4 patients who received antipsychotic medications had improved, whereas 1 patient's condition had worsened; however, the specific CGI-I values were not included. Additionally, of the 10 patients who were not lost to follow-up, antidepressant medications had been administered to a total of 7 patients. Only 3 patients demonstrated benefit as measured by a decrease in depression symptoms; however, objective measures on this outcome were not included in the publication.[9]

Duggan et al[10] conducted a systematic review of randomized controlled trials of the use of pharmacologic treatments for patients with personality disorders. The meta-analysis of 35 trials favored the use of anticonvulsants to reduce aggression and antipsychotics to reduce cognitive perceptual and mental disturbances. Paranoid thinking and ideation fell under the cognitive perceptual domain, yet no study included was actually conducted with a patient who had paranoid personality disorder; rather, paranoid ideation was an outcome listed secondary to borderline personality disorder (a cluster B personality disorder).

Unfortunately, the extreme scarcity of research leaves the question open as to what pharmacologic treatment may or may not be effective for paranoid personality disorder. At this time, perhaps the best option may be to treat the emergent symptomatology in patients with paranoid personality disorder. Ongoing study is needed to further direct pharmacotherapy for the treatment of paranoid personality disorder. At this time, a Cochrane Review is being conducted on the effectiveness of all pharmacologic interventions used in the treatment of paranoid personality disorder.[11] Perhaps this review will offer guidance into further treatment options.

Schizoid Personality Disorder

Schizoid personality disorder is described in DSM-5 as a pattern of detachment from social relationships and a restricted range of emotional expression (Table).[1] Schizoid personality disorder is considered uncommon in clinical settings and may be the least common of the cluster A disorders.[1,12] It is estimated that schizoid personality disorder is prevalent in 0.5% to 7% of the general population and up to 14% in the homeless population.[7] Schizoid personality disorder has been associated with both psychiatric and medical disorders, including dysthymia, mania, panic disorder with agoraphobia, social phobia, generalized anxiety disorder, violent behavior, arthritis, obesity, and coronary artery disease.[13] It has even been suggested by some researchers and clinicians that patients with schizoid personality disorder may be classified into two distinct classification groups of *affect constricted* or *seclusive*, and therefore could be classified under other personality disorder diagnoses, such as schizotypal personality disorder or avoidant personality disorder, respectively.[13]

Conducting a primary literature search for pharmacologic treatment in schizoid personality disorder yields no individual results and is typically categorized with all other personality disorders. The focus of pharmacologic treatment of personality disorders is based on patient-specific symptoms—for example, many of the symptoms of schizoid personality disorder are similar to the negative symptoms in schizophrenia.[14]

The lack of literature regarding pharmacotherapy is most likely contributable to the reclusiveness of these patients and the difficulty in establishing and maintaining a therapeutic relationship.[7] Overall, pharmacologic treatment could be considered in patients with schizoid personality disorder if there are other comorbid psychiatric disorders requiring treatment.

Schizotypal

Individuals with schizotypal personality disorder often feel uncomfortable relating to other people, and although they may express displeasure about a lack of relationships, their behavior suggests a lack of desire for close interactions (Table). These individuals are often anxious in social situations, especially with unfamiliar individuals, which make large studies of patients with schizotypal personality disorder challenging. Although the reported rates of schizotypal personality disorder range from 0.6% to 4.6% of the population, only an estimated 0% to 1.9% of individuals present to the health care setting.[1]

Literature regarding pharmacotherapy for schizotypal personality disorder is limited to small studies that examine olanzapine, risperidone, haloperidol, thiothixene, and fluoxetine. These studies were commonly confounded by the addition of patients with borderline personality disorder.[15-19]

Keshavan et al[18] conducted an open-label study of olanzapine in 11 patients with schizotypal personality disorder in 2004. Only 8 of 11 patients completed the 26-week study; however, an intent-to-treat analysis was used. Study noncompletion was due to lack of follow-up and the need for multiple medications to stabilize the patient's psychiatric condition. Significant improvements were seen in positive and negative symptoms, depressive symptoms,

and overall level of functioning based on the Brief Psychiatric Rating Scale, Hamilton Depression (HAM-D) scale, and Global Assessment Scale (GAS). No significant extrapyramidal symptoms were observed. Additionally, no significant changes in liver function tests, complete blood counts, or electrocardiograms were detected. However, significant weight gain was observed, with an average gain of 7.33 $\pm$ 9.6 kg. Major study limitations included the open-label design, inclusion of comorbid psychiatric disorders, small sample size, concomitant use of divalproex and sertraline by a study subject, and lack of comprehensive evaluation of metabolic complications (blood glucose, cholesterol, etc).

Koenigsberg et al[17] conducted a 9-week, randomized, double-blind, placebo-controlled trial of risperidone in 25 patients with schizotypal personality disorder in 2003. This study excluded patients with borderline personality disorder as a primary diagnosis, as well as patients with schizophrenia or bipolar disorder. However, patients commonly had secondary personality disorders. Investigators obtained weekly symptom measurements by means of the Positive and Negative Syndrome Scale (PANSS). The PANSS total score declined during the 9-week trial period in the treatment group but did not decline in the placebo group. Patients in the treatment group had significantly lower PANSS total scores than the placebo group at weeks 3, 5, 7, and 9. Patients in the treatment group exhibited significantly lower PANSS negative scores versus placebo at weeks 3, 5, and 7. However, the treatment group did not exhibit lower PANSS negative scores versus placebo at week 9. There were several major limitations to the study, including a high rate of secondary personality disorders, a small sample size, an error in the randomization process, and a high dropout rate. Additionally, because of the stepwise dosing of risperidone, it was difficult to determine whether improvement at certain weeks was due to an increase in dose or an increased length of treatment.

A double-blind study conducted by Serban and Siegel[15] in 1984 examined either low-dose thiothixene or low-dose haloperidol in 52 patients with chronic schizotypal and/or borderline personality disorder. The study demonstrated efficacy of both drugs across all diagnoses, with thiothixene exhibiting a greater response than haloperidol. The Psychiatric Assessment Interview revealed statistically significant symptom improvement from baseline to end point within each treatment group for all factors tested, which included general symptoms, anxiety, depression, derealization, paranoia, and ideas of reference. Thiothixene produced statistically significant improvement in general symptoms, depression, and paranoia compared with haloperidol. There was no significant difference between the drugs on the HAM-D scale, but each treatment group improved significantly from baseline to end point. Major limitations of the study included the confounder of patients with borderline personality disorder and the lack of a control group.

A double-blind, placebo-controlled study, conducted by Goldberg et al[16] in 1986, examined thiothixene or placebo in 50 patients with borderline and/or schizotypal personality disorder during the course of 12 weeks. All patients had at least 1 psychotic symptom, and 40% of patients had both schizotypal and borderline personality disorder. The Schedule for Interviewing Borderlines (SIB) was used to evaluate patients weekly. The GAS was used to evaluate patients as well. No significant differences were seen in borderline or schizotypal clusters for the SIB or GAS. Major limitations of this study were a small sample size and the inclusion of patients with borderline personality disorder. Additionally, the symptoms evaluated were clustered into 4 domains that included schizotypal criteria, borderline criteria, SIB criteria psychotic in nature, and miscellaneous. Therefore, the analysis was not designed to look at specific symptoms within these domains, which may have shown differences.

A 12-week, prospective, nonblind study of fluoxetine in patients with borderline and/or schizotypal personality disorder was conducted in 1991.[19] The study consisted of individuals who presented to clinic on their own behalf with symptoms of anxiety or depression. A total of 13 patients had a diagnosis of Major Depressive Disorder (MDD), and 10 patients were receiving psychotherapy. A total of 12 patients reported self-mutilating behavior at baseline. By week 9 of the study, 50% fewer individuals were self-injurious, and the total number of self-mutilative episodes had decreased by 74%. By week 12, only 2 patients were still engaged in cutting behaviors, and these occurred less than one time per week. The Hopkins Symptom Checklist (HSCL) mean score was used to assess symptoms of depression and anxiety. The mean scores at weeks 3, 6, and 9 indicated a progressive decline in symptom severity. However, it was not until week 12 that patients consistently noted improvement. The changes in HSCL scores were similar across personality disorder diagnoses. The presence or absence of MDD did not appear to affect scores at the end point. However, higher baseline scores, indicating greater symptom severity, were seen in the MDD group. There were many limitations of this study, including the self-reported nature of all end points, relevance of end points for schizotypal personality disorder, nonblinded and per-protocol design, and use of lorazepam and chloral hydrate to treat insomnia. Additionally, the inclusion of patients with borderline personality disorder, concomitant MDD, and patients receiving psychotherapy can be considered study limitations.

Interestingly, 3 studies have been conducted in schizotypal patients examining the effect of pharmacotherapy on

negative symptoms. The negative symptoms assessed in these studies included context processing, cognitive deficits, and working memory. McClure et al[20] conducted a 4-week, randomized, double-blind, placebo-controlled study of the effects of guanfacine on context processing abnormalities. This study demonstrated that subjects in the guanfacine group made less errors related to context processing, to a statistically significant degree, compared to the placebo group. The authors concluded that guanfacine may help improve some cognitive deficits seen in the schizophrenia spectrum. McClure et al[21] conducted a 4-week, double-blind, placebo-controlled study on the effects of pergolide on cognitive deficits associated with schizotypal personality disorder. Patients exhibited statistically significant improvements in processing speed, executive functioning, working memory, and verbal learning and memory. Rosell et al[22] conducted a study of the effects of dihydrexidine, a selective D_1 dopamine receptor agonist, on working memory in 16 patients with schizotypal personality disorder. This study showed improved working memory during 1 of the 2 tests administered. It is important to consider that pergolide is no longer available in the United States because of an increase in valvular heart defects. Additionally, dihydrexidine is only available in intravenous formulation and has a short duration of action. Finally, all 3 of the medications investigated in this area affect norepinephrine or dopamine in the prefrontal cortex, which poses the possibility of interactions with antipsychotic medications. Limitations of these studies include small sample size, adverse effects of interventions, and lack of availability of agents.

Overall, olanzapine, risperidone, thiothixene, haloperidol, and fluoxetine exhibited beneficial effects in patients with schizotypal personality disorder. Unfortunately, many of the studies were confounded by the inclusion of patients with borderline personality disorder. As described above, the various limitations of the existing literature require practitioners to apply these findings to clinical practice with caution.

Conclusion

Despite the impact that a cluster A personality disorder may have on an individual, limited research is available regarding pharmacologic treatment. As noted in the paranoid personality disorder section, there are several proposals for why there may be a lack of research. Generally, patients with a cluster A personality disorder tend to be isolative and may not readily seek medical attention. Therefore, they may not be easily recruited into research studies. Additionally, certain traits of each personality disorder—schizotypal, schizoid, and paranoid—may be unfavorable to a study, that is, difficulty in developing a therapeutic relationship and continuity of care.

Overall, most of the literature found was for the treatment for schizotypal personality disorder. As illustrated in "Methods," the most search terms were used when reviewing data for schizotypal personality disorder, which has the potential to bias the results. However, the additional searches were completed after discovering information concerning schizotypal personality disorder and specific medications. No specific medication information was found using the basic searches for paranoid personality disorder or schizoid personality disorder, so further search terms were not indicated. Even with the greater number of articles for schizotypal personality disorder, the literature has limitations. The use of olanzapine, risperidone, haloperidol, fluoxetine, and thiothixene did yield beneficial results in patients with schizotypal personality disorder; however, treatment with such agents should be considered on a case-by-case basis.

The literature review conducted on paranoid personality disorder and schizoid personality disorder yielded no controlled trials. There was a single case series of treatment of paranoid personality disorder in Denmark, but there were no conclusive results to guide future treatment recommendations beyond the tentative conclusion that an antipsychotic may be beneficial. Similarly, because of the complete lack of evidence for schizoid personality disorder, no recommendation for pharmacotherapy treatment can be offered at this time.

In conclusion, most of the literature analyzed in this review presented theoretical ideas of what may constitute the neurobiologic factors of personality and what treatments may address these aspects. Further research is needed to evaluate specific pharmacologic treatment in the cluster A personality disorders. At this time, treatment with pharmacologic agents is based on theory rather than evidence.

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