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Review

Sexual Dysfunction in Schizophrenia: A Narrative Review of the Mechanisms and Clinical Considerations

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Abstract: Psychiatric disorders, in general, have a high prevalence of sexual problems, whether from the psychopathology of the disorder itself, pre-existing or co-morbid sexual disorder or from side effects of the treatment for mental disorders. Many patients report an already existing sexual dysfunction at the onset of diagnosis. The risk association for developing sexual dysfunction in patients with schizophrenia includes antipsychotic use and resulting hyperprolactinemia, age, gender, and disease severity. Medication side effects lead to nonadherence, and relapses lead to structural changes in the brain, treatment resistance, and worsening of symptoms. Findings in certain studies propose serum prolactin and thyroid-stimulating hormone measurement as a tool for assessing patients with schizophrenia for sexual dysfunction. Regarding specific symptoms, females especially reported decreased desire at baseline and galactorrhea after treatment. The findings of this review, therefore, suggest that sexual dysfunction may be present in patients with schizophrenia before starting antipsychotic treatment and that patients, especially those who are female, are likely to develop hyperprolactinemia with antipsychotic treatment. Aripiprazole may be an emergent treatment for sexual dysfunction in those who use antipsychotics. It is important for patients to consider sexual dysfunction prior to prescribing antipsychotics. Since sexual dysfunction can impact a patient's quality of life and affect treatment adherence, it is important for physicians to be aware and monitor patients for symptoms.

Keywords: antipsychotics; sexual dysfunction; prolactin; thyroid-stimulating hormone; schizophrenia

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1. Introduction

Psychiatric disorders have a high prevalence of sexual problems, whether from the psychopathology of the disorder itself, pre-existing or co-morbid sexual disorder, or from side effects of the treatment for mental disorders [1,2]. In schizophrenia, negative symptoms (anhedonia) can attribute to decreased sexual functioning [1,3]. Males and females with schizophrenia have reported sexual dysfunction in the form of decreased sexual desire, decreased sexual arousal (erectile dysfunction, priapism, diminished vaginal lubrication), anorgasmia, ejaculation, and menstrual disturbance, galactorrhea, or gynecomastia [3]. A study conducted by Serretti et al. showed that 16–60% of patients using antipsychotics reported sexual dysfunctions [3,4]. Antipsychotic medications may cause decreased sexual desire, erectile dysfunction, anorgasmia, and delayed or retrograde ejaculation [5,6]. This is in accordance with what is reported by patients with Schizophrenia as stated earlier in the paragraph. Patients with schizophrenia consider sexual problems to be very important

related to the effects on quality of life and adherence to medication. Discussing sexual problems with a provider is sometimes difficult for patients. Physicians should be aware of this and initiate conversations about their patient's sexual histories and expectations for their sexual life before prescribing antipsychotic medications [2,3]. The sexual side effects of medications may be the reason many people discontinue them. The aims of this review are to discuss the possible medication causes of sexual dysfunction, to examine sexual dysfunction in general as it exists in patients with a psychotic disorder, and to highlight possible interventions, such as aripiprazole as an adjunctive treatment for sexual dysfunction caused by hyperprolactinemia.

1.1. Schizophrenia Overview

The most reported symptoms at the onset of the prodromal phase are restlessness, depression, anxiety, insolation, or difficulty concentrating. The psychotic phase is marked by the onset of a positive symptom, such as hallucinations or delusions [7,8]. Clinical symptoms of schizophrenia have traditionally been categorized as positive or negative symptoms. Positive symptoms include delusions, hallucinations, disorganized speech such as incoherence, disorganized behavior, and catatonic behavior. Negative symptoms include anhedonia, flat affect, lack of motivation, alogia, and a deficit of attention [9]. DSM-5 criteria include at least one of the following: delusions, hallucinations, disorganized speech. Additionally, the patient must have at least one additional symptom, either delusions, hallucinations, disorganized speech, or one of the following: disorganized behavior, catatonic behavior, negative symptoms. Negative symptoms are important to assess and track. Functional impairment often stems from the persistence of negative symptoms even after positive symptoms have yielded [9].

Knowing these symptoms are important to understand the treatment, as much of the treatment focuses on the dopamine system. Dopamine in the mesolimbic system has been thought to be responsible for the positive systems of schizophrenia. Dopamine in the mesocortical system is thought to be responsible for the negative systems [10]. This has been the traditional target of the treatment of schizophrenia and has also been implicated in side effects such as dystonia and sexual dysfunction.

1.2. Current Treatment of Schizophrenia and Treatment Side Effects

It is thought that the symptoms of schizophrenia are a result of dopaminergic dysfunction in the mesolimbic and mesocortical pathways of the brain. Positive symptoms, such as delusions and hallucinations leading to psychosis, are attributed to excess dopamine activity in the mesolimbic pathway. Negative symptoms are thought to be a result of reduced dopamine signaling in the mesocortical pathway [11]. The dopamine dysregulation hypothesis is supported by the success of D2 receptor antagonism in reducing psychotic symptoms and D2 agonists, such as amphetamines, inducing psychosis [12]. The mainstay of treatment for schizophrenia has been antipsychotic medications whose mechanism of action is through D2 receptor inhibition. A reduction of psychotic symptoms occurs when there is more than 65% occupation of striatal D2 receptors. Increased occupation of receptors does not improve the antipsychotic properties of the drug, but increases the risk of extrapyramidal side effects (EPS) and hyperprolactinemia with an occupation of ~80% and 72%, respectively [13]. These side effects are associated with striatal dopaminergic blockage, whereas therapeutic effects occur mainly in the mesolimbic system [11].

Antipsychotic medications can be separated into generations by their mechanism of action and side effect profiles. First to be developed, the first-generation antipsychotics (FGA), also called "typical", can be further separated based on potency in binding to the dopamine D2 neuroreceptor [11,14]. Low potency FGAs include chlorpromazine and thioridazine. High potency FGAs include drugs such as haloperidol, fluphenazine, thiothixene, trifluoperazine and pimozide [14,15]. The FGAs are D2 receptor antagonists. Considered "atypical" due to their targeting of receptors other than just D2, the second-generation antipsychotics (SGA) were the next to be developed. Drugs included in this

class are paliperidone, clozapine, olanzapine, quetiapine, risperidone and ziprasidone. These medications act on a variety of receptors including D1, D2, D3, D4, adrenergic alpha1 and alpha2, serotonin $5HT_{2A}$ and $5HT_{2C}$, histamine, and muscarinic receptors leading to a differing side effect profile when compared to FGAs [15]. Third-generation antipsychotics—aripiprazole, brexpiprazole, cariprazine—are selective or partial D2 agonists with some effects on $5HT_{1A}$ and $5HT_{2A}$ [16].

Due to the dopaminergic blockage of antipsychotic medications, most recognizably FGAs and some SGAs, such as risperidone and paliperidone, are associated with asymptomatic or symptomatic hyperprolactinemia leading to gynecomastia, galactorrhea, oligo- or amenorrhea, acne, hirsutism, infertility, and loss of bone mineral density causing osteoporosis with increased risk of fracture [17–20]. Another potential cause of medication noncompliance is the associated sexual dysfunction patients on antipsychotics experience. Erectile and ejaculatory dysfunction in men, along with a reduction in libido, sexual arousal, and orgasm in both men and women, have been found in those taking FGAs and SGAs [21–23]. SGAs are associated with metabolic syndrome derangements, the greatest risk found with clozapine and olanzapine. Rapid weight gain that is difficult to manage, poor glycemic control, insulin resistance, diabetic ketoacidosis, and dyslipidemia leading to hypertriglyceridemia can all be attributed to these antipsychotics [24–26]. Clozapine is the only medication proven to be effective at treating treatment-resistant schizophrenia and may cause neutropenia/agranulocytosis leading to potentially fatal infections [27,28].

Medication side effects lead to nonadherence, and relapses lead to structural changes in the brain, treatment resistance, and worsening of symptoms. It is important for providers to monitor compliance with treatment in order to prevent adverse developments in the patient's condition [29]. Options such as long-acting injection (LAI) medications are available for those who prefer them or for patients that are nonadherent to their treatment. Conflicting studies report the effectiveness of LAIs, with some showing a reduction in relapse and rehospitalization, whereas others did not [30–32].

1.3. Sexual Dysfunction in Psychiatric Conditions

The prevalence of sexual dysfunction in multiple psychiatric conditions and as a consequence of pharmacologic management of those conditions has been described in the literature. Patients with major depressive disorder often report reduced sexual desire and erectile dysfunction. Anxiety disorders such as panic attacks, social phobia, and obsessive-compulsive disorder have also been shown to be highly associated with sexual dysfunction disorders. Eating disorders and certain personality disorders, such as histrionism, have also been shown to be associated with sexual dysfunction. Perhaps more studied are the sexual dysfunctions that arise from the pharmacologic management of psychiatric conditions. Anti-psychotics and anti-depressants are well-known to lead to various sexual dysfunctions [1]. Anti-epileptic drugs are also shown to have sexual dysfunction side effects [33].

Recently, the neuroanatomy and neurotransmitters that modulate sexual behavior have been described. The thalamus, hypothalamus, amygdala, septal region, prefrontal cortex, cingulate cortex, and insula all play important roles in receiving, modulating, and transmitting sensory signals for sexual drive. Furthermore, the neurotransmitters and structures involved in the reward pathway, such as dopamine, GABA, nucleus accumbens, orbitofrontal cortex, dorsal anterior cingulate cortex, and the ventral tegmental area, play an important role in sexual desire [34]. Abnormalities in many of these intracranial structures and neurotransmitters have been shown to play a role in the pathophysiology of schizophrenia. It stands to reason, therefore, that patients with schizophrenia would have significant sexual dysfunction.

1.4. Sexual Dysfunction in Psychotic Disorders

In patients with psychosis, in general, there is thought to be a dysfunction in sexuality. This relates to the patient having a disruption in their theory of mind [35]. This is the ability

to understand what others are thinking and feeling in terms of their mental states. This disruption will interfere with the person's ability to form interpersonal relationships. These relationships are important to form sexual partnerships. Physicians fail to evaluate patients with psychosis for sexual dysfunction at baseline, which has a significant impact on the patient's quality of life [36]. A recent review found that those at high risk for psychosis who developed full-blown psychosis had a higher level of sexual dysfunction than those who were at high risk but did not develop full-blown psychosis [37]. This baseline sexual dysfunction, which could be worsened by antipsychotic treatment, could be a significant risk factor for patients even at risk for developing full-blown schizophrenia as it impacts treatment adherence.

With regard specifically to sexual dysfunction in schizophrenia, research has primarily focused, as mentioned before, on the sexual dysfunction side effects of common antipsychotics. The prevailing theory is that second-generation anti-psychotics lead to less sexual dysfunction than their first-generation counterparts due to a lesser degree of prolactin elevation. Studies, however, are limited by small sample sizes and different assessment scales of sexual dysfunction [38]. The prolactin levels are usually associated with menstrual cycle irregularities and erectile dysfunction. High prolactin levels interfere with the production of hormones such as estrogen and progesterone, which can cause menstrual irregularities [39]. High prolactin levels are also associated with decreased testosterone, which is associated with erectile dysfunction as well as decreased sex drive in females [40].

Further complicating this discussion is that patients with schizophrenia often present with varying sexual dysfunction prior to treatment. One study finds that only 53% of patients diagnosed with schizophrenia report a prior sexual encounter, and only 41.3% report active sexual intercourse. Furthermore, 59.3% of patients reported existing concurrent sexual dysfunction at the onset of diagnosis [41].

2. Selection of the Studies/Methods

This section aims to highlight how studies in the following section were selected. PubMed was used for the selection of the studies. Keywords included were sexual dysfunction and psychotic disorders along with sexual dysfunction and medication side effects. If studies were clinical in nature and involved patients as subjects, they were included in the review. Other studies that were review articles were scanned for primary sources that were not found in the original PubMed search. These primary clinical studies were also included in the section below. PubMed was the only database used and the literature search was performed between 20 February and 25 February 2021. Scopus, Web of Science and Embase were not used as the authors did not have access to these databases.

The treatment of sexual dysfunction in psychotic disorders was also searched for in PubMed. The terms "treatment", "sexual dysfunction", and "psychotic disorders" were used to search for related studies. Studies that were clinical trials were included in the section below. The inclusion criteria for this manuscript include randomized controlled trials, cross-sectional studies, and observational studies. Excluded studies included review papers. English language papers were the only papers included as well.

3. Results

An inpatient cross-sectional study measured the levels of prolactin and thyroid-stimulating hormone (TSH) as well as sexual dysfunction in 118 patients (55 males and 63 females) with schizophrenia treated with antipsychotics. Additionally, luteinizing hormone (LH), estradiol (E2), progesterone, testosterone, triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4) levels, and various other labs were measured in these same patients. The authors measured sexual dysfunction using the Arizona Sexual Experience Scale (ASEX) and found that most patients (91.8%) with sexual dysfunction also had elevated prolactin levels. Increased levels of prolactin were found in only 17.5% of patients without sexual dysfunction. The median prolactin levels were 1018.0 mIU/L and 226.7 mIU/L for the sexual dysfunction group and the non-sexual

dysfunction group, respectively, demonstrating a significant difference ($p < 0.01$) between the two groups. A significant difference between the two groups was also found when comparing TSH levels. Median TSH levels were 2.70 mIU/L in the sexual dysfunction group and 2.06 mIU/L in the non-sexual dysfunction group. The authors state that this is the first study to investigate the relationship between subclinical hypothyroidism and sexual dysfunction in patients with schizophrenia and sexual dysfunction. Mean red blood cell values, hemoglobin, and creatinine levels were significantly decreased in patients with sexual dysfunction. However, creatinine levels were normal in both groups. Additionally, patients with sexual dysfunction were more likely to be female and to have higher severity of disease, as assessed using the Positive and Negative Syndrome Scale (PANSS). No difference between the sexual dysfunction group and the no sexual dysfunction group was found for age, marital status, age at disease onset, or levels of T3, T4, FT3, FT4, FSH, LH, E2, blood urea, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), white blood cells (WBCs), and platelets (PLT). Considering these findings, the authors of this study proposed serum prolactin and TSH measurements as a tool for assessing patients with schizophrenia for sexual dysfunction. The authors additionally hypothesize that increased hemoglobin and red blood cell levels, which increase oxygen-carrying capacity, may be protective for sexual dysfunction in patients with schizophrenia and encourage further studies in these areas [42].

It has not previously been clear whether high levels of prolactin develop from causes other than antipsychotic use, nor has the degree to which sexual dysfunction is directly caused by increased serum prolactin been completely understood. A 2019 study compared prolactin levels and sexual functioning in 65 patients with schizophrenia at baseline and after 6 months of antipsychotic treatment. Although limited in its sample size, this study found sexual dysfunction in 68% of patients with schizophrenia at baseline and in 65% of patients after antipsychotic treatment. After treatment with the D2/3 receptor blockader, amisulpride, all 36 follow-up patients developed hyperprolactinemia. Only 11% of males and 10% of females at baseline had increased prolactin levels. The mean sexual dysfunction, measured using the Udvalget for Kliniske Undersogelser (UKU) questionnaire, found a significantly higher degree of sexual dysfunction in females compared to males, both at baseline and after six weeks of treatment. Regarding specific symptoms, females especially reported decreased desire at baseline and galactorrhea after treatment. Findings of this study therefore suggest that sexual dysfunction may be present in patients with schizophrenia before starting antipsychotic treatment and that patients, especially those who are female, are likely to develop hyperprolactinemia with antipsychotic treatment [43].

Another cross-sectional from 2017 assessed the magnitude of, and factors contributing to, sexual dysfunction in 422 patients (290 male and 132 female) with schizophrenia. Sexual dysfunction was measured using the Changes in Sexual Functioning Questionnaires (CSFQ-14), quality of life was assessed using the WHOQOL-BREF, depression was evaluated using the PHQ-9, and the Morisky medication adherence scale was used to measure patient adherence to antipsychotic medication. The most common antipsychotics used by patients in this study were chlorpromazine and risperidone (used in 43.6% and 26.3% of patients, respectively). The prevalence of sexual dysfunction among participants was 82.7% overall. In males, the prevalence of sexual dysfunction was 84.5%. The prevalence of erectile dysfunction was 95.2% and pleasure dysfunction was 94.2%. In females, the prevalence of sexual dysfunction was 78.6%. The prevalence of pleasure dysfunction in females was 94.7%, and the prevalence of arousal/excitement dysfunction was 93.2%. Sexual dysfunction was associated with a decreased quality of life. Unmarried participants were four times more likely to experience sexual dysfunction and widowed or divorced participants were three times more likely to experience sexual dysfunction. Patients who had a history of relapse, characterized by deterioration, an increase in negative symptoms, or a need for an increase in antipsychotic medications, were also more likely to develop sexual dysfunction [44].

A 2019 cross-sectional study explored sexual dysfunction in and the quality of life of 720 Chinese rural patients with schizophrenia [45]. Sexual dysfunction was measured using the Arizona Sexual Experience Scale (ASEX) and defined as any patient with a sexual partner who has a total ASEX score of 19 or higher. Patients without sexual partners answered a smaller set of questions, and sexual dysfunction in these patients was thus defined as having an ASEX score of 5 or higher. Psychotic symptoms were estimated using the Brief Psychotic Rating Scale (BPRS), depressive symptoms were estimated using the Chinese version of the Montgomery–Asberg Depressive Rating Scale (MADRS), extrapyramidal symptoms were estimated using the Angus Scale of Extrapyramidal Symptoms (SAS), and quality of life was measured using the Chinese version of the WHOQOL-BREF which assess quality of life in the physical, psychological, social and environmental domains. Of the 720 patients studied, sexual dysfunction was found in 71.3% of those who did not have sexual partners and in 74.1% of patients with sexual partners. Sexual dysfunction in the group without sexual partners was found in 64.5% of males and 82.7% of females. Sexual dysfunction in the group with sexual partners was found in 67.8% of males and 82.1 % of females. Significant differences were found in comparing BPRS total scores and MADRS scores of the sexual dysfunction group and the non-sexual dysfunction group. No difference with regards to extrapyramidal symptoms or physical, psychological, social, and environmental domains of quality of life was found between the same two groups. However, analyzing single demographics found increased ASEX scores in patients who were older or who had more BPRS negative symptoms. In sum, this study agrees with other studies that have found increased sexual dysfunction in patients with schizophrenia, especially in females. In this study, 20–30% of males and 40–45% of females reported at least one item of sexual dysfunction measured by the ASEX scale. The authors attribute these results to multiple potential factors including the sample size, socio-economic and demographic factors, psychopathology, and psychiatric medications used to treat patients with schizophrenia. The study mentions limitations in using tools like the ASEX scale, which was designed to be evaluative rather than diagnostic for sexual dysfunction and the WHO-QOL, which was not designed specifically to measure quality of life for patients with schizophrenia and which only measures quality of life over two weeks prior [45].

Another cross-sectional study sought to evaluate sexual dysfunction and its impact on quality of life in patients with schizophrenia as well as in patients with bipolar disorder and depression using the ASEX scale and the WHO-QOL [46]. Patients studied were male, between 20–60 years old, married, heterosexual, and clinically stable with regards to symptoms and treatment. The sample consisted of 30 patients with bipolar disorder and depression and 19 patients with schizophrenia. There were 50 healthy controls. Rates of sexual dysfunction were high in the patient groups when compared to the controls. The patient groups experienced higher rates of sexual dysfunction, with a mean ASEX score of 19 compared to the control group who had a mean score of 5. In examining specific components of the ASEX scale, the study found that patient groups had higher scores (greater dysfunction) for sexual drive, arousal, penile erection, ability to reach orgasm, and, except for the schizophrenia group, satisfaction with orgasm. In addition, older age was associated with a higher ASEX score. In measuring the quality of life, however, the study found that patients with schizophrenia and bipolar disorder and depression had increased quality of life scores estimated using the WHO-QOL tool in the areas of psychological status, physical health, and environmental conditions. No difference was found compared to the control group in the quality of life area of social relations and in one question asking about sexual satisfaction [46].

A high prevalence of sexual dysfunction was found in a 2018 cross-sectional study from Spain [47]. Sexual dysfunction, measured using the seven-item Psychotropic-Related Sexual Dysfunction Questionnaire (PR SexDQ-Salsex), was demonstrated in 80% of the 57 outpatients with schizophrenia included in this study. Participants included in the patient group were adults 18–65 years old with schizophrenia and had been treated with second-generation antipsychotic monotherapy for at least 6 months. Interestingly, only

30% of those 80% of outpatients spontaneously reported having any issue with sexual dysfunction during clinical assessment, demonstrating in the view of the authors a need for a more tailored approach to assessing and addressing sexual dysfunction in patients with schizophrenia by healthcare professionals. No significant difference was found when comparing the relationship between sexual dysfunction and specific antipsychotic medications received by the patient group. Socioeconomic and clinical characteristics of the patients in the study were analyzed. Every 10 additional years of age was associated with a 1.3× increase in likelihood of sexual dysfunction in this study's patient group. Patients who were single or divorced were also more likely to report sexual dysfunction. This study also examined but did not find any relationship between hyperprolactinemia, testosterone, estradiol and progesterone levels and sexual dysfunction. However, the study did find it significant that patients taking aripiprazole had a decreased mean serum prolactin of level 3.98, while patients taking risperidone/paliperidone had an increased mean serum prolactin level of 30. Limitations of this study include its small sample size and inclusion bias, because patients with lower disease severity, who were likely more stable, were chosen for this study [47].

Some clinical studies have looked more specifically at the relationship between sexual dysfunction and antipsychotic use in 87 patients with schizophrenia. A study by Kikuchi et al. found a higher prevalence of sexual dysfunction (using the Nagoya Sexual Function Questionnaire (NSFQ)) and hyperprolactinemia in Japanese schizophrenia [48]. In this study the serum prolactin was elevated in 31.4% of female patients and. 27.8% of male patients. In this study, approximately 50% of the patients reported some degree of sexual dysfunction. The patients reporting sexual dysfunction had a significantly higher serum prolactin level compared to those patients who did not report any sexual dysfunction (mean serum prolactin = 21.43 vs. 9.18) [48]. For patients treated with monotherapy, those taking aripiprazole were more likely to have lower mean serum prolactin levels compared to those patients taking other antipsychotics (mean serum prolactin = 9.60 vs. 29.24). For patients taking 2 or more antipsychotics, if aripiprazole was part of their regimen, patients were more likely to have decreased mean prolactin levels compared to those on regimens not including aripiprazole (mean serum prolactin = 8.10 vs. 31.48). Hyperprolactinemia was highly prevalent among the patients studied (male 51.3% and females 53.8%) with female patients showing extremely high prolactin concentration levels (16.7% > 100 ng/mL) [48].

4. Analysis of Studies

Recent clinical studies have attempted to better understand sexual dysfunction in patients with schizophrenia. Studies typically evaluate the degree of sexual dysfunction through self-administered questionnaires filled out by patients with schizophrenia. The commonly used Arizona Sexual Experience Scale (ASEX), for example, measures sexual function through a 5-item scale which explores strength of sexual drive, ease of sexual arousal, penile erection or vaginal lubrication, the ability to reach orgasm, and satisfaction with orgasm in the past week [42,45,46]. Other measurement tools for sexual dysfunction include the Psychotropic-Related Sexual Dysfunction Questionnaire, the Changes in Sexual Functioning Questionnaires (CSFQ-14) and the Udvalg for Klinsike Undersogelser (UKU). Some researchers conducting clinical studies have also developed their own questionnaires that explore similar factors of sexual functioning [43,44,47,49]. The 2011 Japanese study evaluating sexual dysfunction in schizophrenic patients used a custom 7-item questionnaire called the Nagoya Sexual Function Questionnaire (NSFQ) in order to better tailor the style of questions asked to the sensitivities of Asian patients with schizophrenia, who are often culturally more hesitant to discuss matters of sexual functioning with their physicians. NSFQ questions were designed and intended to be less invasive and more likely to elicit a response from patients assessed [48]. Despite the range of tools used to measure sexual functioning, studies consistently find a significant proportion of sexual dysfunction among schizophrenic patients. Sexual dysfunction is estimated to affect a significant number of

patients suffering from and treated for schizophrenia [44,45,49] with prevalence estimates ranging from around 30% to as high as 83% in different studies [42,43,47].

Although the precise mechanism of the development of sexual dysfunction is unknown, the relationship between several variables believed important in the cause of sexual dysfunction in patients with schizophrenia have been evaluated in cross-sectional studies. These variables include prolactin levels, quality of life, antipsychotic medication, gender, and disease severity. Although these studies do not always completely agree in their findings, there have been some significant correlations shown across multiple studies with regards to certain variables, most notably gender, antipsychotic use, and prolactin levels.

Hyperprolactinemia has been established as a well-known side effect of antipsychotic medications used to treat schizophrenia, due to the disruption of the tuberoinfundibular pathway via dopamine blockade. In particular, risperidone/paliperidone and olanzapine have the most profound impact on prolactin levels [47,49]. In contrast, the second-generation antipsychotic aripiprazole (APZ) has been associated with decreased prolactin levels and is thought to stabilize D2 receptor-mediated neurotransmission through non-excessive receptor blockade [47]. A study by Kirino et al found a decrease or resolution of hyperprolactinemia in patients treated for schizophrenia with APZ monotherapy or with polytherapy including APZ. Serum prolactin was additionally found significantly higher in patients experiencing at least one symptom of sexual dysfunction compared to those who did not [49]. It has not been clear whether high levels of prolactin develop from causes other than antipsychotic use, nor has the degree to which sexual dysfunction is directly caused by increased serum prolactin been completely understood. Examining these questions, During et al compared prolactin levels and sexual functioning in patients with schizophrenia at baseline and after 6 months of antipsychotic treatment [43]. This study found sexual dysfunction in 68% of patients with schizophrenia at baseline and 65% after treatment. After treatment with D2/3 receptor blockade amisulpride, all patients developed hyperprolactinemia. Only 11% of males and 10% of females at baseline had increased prolactin levels [43]. Recent clinical studies show the importance in considering the relationship between hyperprolactinemia and sexual dysfunction in schizophrenia patients and suggest that monitoring baseline and follow-up levels of prolactin in patients may allow for better management of sexual dysfunction in patients, especially in those treated with antipsychotics known to cause hyperprolactinemia [43,47,49].

Studies have also found a higher incidence of sexual dysfunction in female patients [43,47,49]. For example, Düring et al. found high levels of sexual dysfunction in females and males both before and after antipsychotic treatment. After treatment, however, sexual dysfunction in females was significantly higher compared to males [43]. Increased levels of sexual dysfunction typically coincide with pronounced serum prolactin levels in female patients. Kikuchi et al. as well as Kirino et al. found that a proportion of female patients experienced particularly high levels of prolactin (>100 ng/mL) [48,49]. These patients were found in the Kirino study to experience irregular menstruation or amenorrhea [49].

Disease severity, quality of life, and age have also been studied for their association with sexual dysfunction in patients with schizophrenia. Older age has also been correlated with increased incidence of sexual dysfunction [45,46], while results studying disease severity and quality of life have shown mixed results. Martin et al. found no relation between severity of schizophrenia and sexual dysfunction, while Zhang et al. found increased disease severity scores, particularly scores impacted by increased negative symptoms, to be an independent factor for the development of sexual dysfunction [43,47]. Ghormode et al. and Huang et al. found that patients with schizophrenia experienced more sexual dysfunction but found no differences in social relationships measured quality of life questionnaires compared to controls [45,46]. Contrastingly, the Ethiopian study found that sexual dysfunction was associated with a poorer quality of life in patients with schizophrenia, hypothesizing that this effect is due to the effect of the disease has on a patient's ability to maintain personal intimate relationships [44]. Additionally, patients in this study who were unmarried,

widowed, or divorced, were 3–4× more likely to develop sexual dysfunction [44]. Table 1 is a summary of the discussed clinical studies.

Table 1. Clinical Studies.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Zhang et al. (2018) [42]	Cross-sectional observational, hospital-based study of 118 patients with a diagnosis of schizophrenia. Measured serum prolactin, follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, testosterone, thyroid-stimulating hormone, triiodothyronine (T3), thyroxine (T4), free triiodothyronine, free thyroxine.	Hyperprolactinemia was found in 66 patients (55.9%). Hyperprolactinemia was found in 91.8% of the sexual dysfunction group and in 17.5 % of the non-sexual dysfunction group ($p < 0.001$) with higher incidence in female patients.	Sexual dysfunction was significantly increased in patients with schizophrenia, especially female patients. Hyperprolactinemia and subclinical hypothyroidism were associated with sexual dysfunction.
Düring et al. (2019) [43]	Cross-sectional study that compared prolactin levels and sexual functioning in 65 patients with schizophrenia at baseline and after 6 months of antipsychotic treatment.	Sexual dysfunction was found in 68% of patients with schizophrenia at baseline and in 65% of patients after antipsychotic treatment. Only 11% of males and 10% of females at baseline had increased prolactin levels. A significantly higher degree of sexual dysfunction was found in females compared to males, both at baseline and after six weeks of treatment	Patients with schizophrenia experience increased levels of sexual dysfunction both before and after antipsychotic use. After treatment females experienced more sexual dysfunction and greater increases in serum prolactin levels.
Huang et al. (2019) [45]	Cross-sectional study that evaluated sexual dysfunction in and the quality of life of 720 Chinese rural patients with schizophrenia. Measured sexual dysfunction using the ASEX scale. Psychotic symptoms were estimated using the Brief Psychotic Rating Scale (BPRS), depressive symptoms were estimated using the Chinese version of the Montgomery-Asberg	Sexual dysfunction found in 71.3% of patients who did not have sexual partners and in 74.1% of patients with sexual partners. Sexual dysfunction in the group without sexual partners was found in 64.5% of males and 82.7% of females. Sexual dysfunction in the group with sexual partners was found in 67.8% of males and 82.1% of females. No difference with regard to extrapyramidal symptoms or physical, psychological, social, and environmental domains of quality of life was found between the same two groups.	Over 70% of schizophrenia patients living in a rural area complained of sexual dysfunction, which was associated with older age and more negative psychotic symptoms.

Table 1. *Cont.*

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Ghormode et al. (2019) [46]	Cross-sectional study of 79 clinically stable patients with schizophrenia compared with 50 healthy controls, Sexual dysfunction estimated using the ASEX scale and quality of life using the WHO-QOL scale, Chi-square test used for the categorical variables and *t*-test for continuous variables	Patients with schizophrenia had higher rates of issues achieving arousal ($p < 0.01$), penile erection ($p = 0.03$), and satisfaction from orgasm ($p = 0.03$).	A significant portion of patients with schizophrenia, bipolar disorder, and depression experience sexual dysfunction.
Martin et al. (2018) [47]	Cross-sectional study of 57 outpatients with schizophrenia, examining sociodemographic information, sexual history, psychotic and depressive pathology and symptoms, metabolic syndrome and BMI. Sexual dysfunction measured using Psychotropic-Related Sexual Dysfunction Questionnaire (PR SexDQ-Salsex); Plasma concentrations of prolactin, testosterone, estradiol, progesterone were also measured.	80% of patients studied experienced sexual dysfunction, with approximately 1/3 experiencing levels of sexual dysfunction considered severe. There were significant differences in the prevalence of hyperprolactinemia and metabolic syndrome depending on antipsychotic treatment. No association was found between sexual dysfunction and prolactin, sexual hormones, type of antipsychotic received, psychotic psychopathology or metabolic syndrome.	Sexual dysfunction was found in high prevalence in patients with schizophrenia. Sexual dysfunction in these patients was associated with higher age, single or divorced status, and depressive pathology. The etiology for sexual dysfunction, then, is multivariate.
Kirino et al. (2017) [49]	Cross-sectional observational study, measuring serum prolactin levels using ELISA and the Nagoya Sexual Function Questionnaire to measure sexual dysfunction in 87 patients with schizophrenia	Serum prolactin was significantly higher in females than males. 27.8% males serum prolactin levels were abnormally high while 31.4% females were. Some females had very high (16.7% with levels > 100 g/dL) prolactin levels. Sexual dysfunction was found in 48.1% of patients studied. Patients receiving 2 or more antipsychotics had lower serum prolactin levels if aripiprazole was included in their treatment regimen (mean serum prolactin = 8.10 vs. 31.48). For patients receiving monotherapy, aripiprazole was associated with significantly lower serum prolactin levels (mean serum prolactin = 9.60 vs. 29.24.	Treatment with aripiprazole did not influence the serum prolactin level, and adjunctive treatment with aripiprazole may decrease hyperprolactinemia that occurs in patients receiving monotherapy with other antipsychotics.

Table 1. *Cont.*

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Kikuchi et al. (2011) [48]	Cross-sectional observational study, examined the prevalence of sexual dysfunction in 195 Japanese in- and out-patients from October 2009 to January 2010 with schizophrenia.	The prevalence of sexual dysfunction in patients with schizophrenia was high (males 66.7%; females 79.5%). Hyperprolactinemia (>25 ng/mL) was highly prevalent among schizophrenia patients, affecting 53.8% of females and 51.3% of males. Among female patients, 16.7% had prolactin levels > 100 ng/mL.	There was a higher prevalence of sexual dysfunction and hyperprolactinemia in Japanese schizophrenia patients.

5. Treatment of Sexual Dysfunction in Schizophrenia

Many of the studies reviewed looked at the treatment of the increased prolactin levels that are caused by antipsychotic therapy. One such study looked at the treatment of hyperprolactinemia using bromocriptine vs. herbal medicine in patients with risperidone-induced hyperprolactinemia [50]. Hyperprolactinemia was diagnosed with serum prolactin levels > 50 mug/L. The subjects were randomized to receive Peony-Glycyrrhiza Decoction (45 g/day) followed by bromocriptine (5 mg/day) or bromocriptine followed by Peony-Glycyrrhiza Decoction. Sexual dysfunction was defined as either experiencing oligomenorrhea or amenorrhea. The severity of psychotic symptoms, adverse events, serum prolactin levels, estradiol, testosterone, and progesterone levels were examined at baseline and endpoint [51]. The authors concluded that Peony-Glycyrrhiza Decoction showed fewer adverse events, and significantly decreased prolactin levels without worsening of psychosis or other hormone levels.

Many studies have looked at the use of aripiprazole to decrease the hyperprolactinemia associated with antipsychotic treatment. One study looked at the addition of 5 mg of aripiprazole to treat hyperprolactinemia associated with the use of an injection form of risperidone [52]. This was an open, uncontrolled trial of 13 patients treated with injectable risperidone. Twelve of the thirteen patients showed a decrease in serum prolactin levels and the eight that continued treatment for two more months continued to show a decrease in prolactin levels [52]. Adverse effects of aripiprazole were transient and mild.

Another Japanese study looked at the use of adjunctive aripiprazole to treat hyperprolactinemia. They found that prolactin levels at week 4 and later was significantly lower than at the beginning of the study, Sexual dysfunction was also significantly improved, which was measured by erectile dysfunction in males and menstrual irregularity [50]. The problem with these studies, however, is their limited sample size and more studies would need to be done to validate the use of aripiprazole in the treatment of hyperprolactinemia and sexual dysfunction in patients using other antipsychotics.

6. Conclusions

Schizophrenia is a chronic illness that, in most cases, is diagnosed early in a patient's life and has the potential to negatively affect their personal and social life. Sexual dysfunction has been shown to affect a significant portion of schizophrenic patients and is associated with a poorer quality of life due to the reduced ability to maintain personal intimate relationships. This dysfunction may be due to the disease itself or may come as a result of pharmacologic treatment. There is a lack of understanding that this can happen at baseline in a patient with a psychotic disorder. A comprehensive review of the patient's sexual health should be done whether it be by a primary care physician, psychiatrist, or

clinical psychologist. Patients may have their relationships affected by this and studies have shown that it leads to a decreased quality of life. Patients who have psychotic disorders may want a family in the future and this is a hinderance to that desire. This could lead to medication non-adherence which will lead to further psychotic breaks and more problems down the road. It can start to be avoided if the clinician thinks about sexual dysfunction in patients with this type of psychiatric condition and screens for it.

Many patients report an already existing sexual dysfunction at the onset of diagnosis. The risk association for the development of sexual dysfunction in patients with schizophrenia includes antipsychotic use and resulting hyperprolactinemia, age, gender, and disease severity. First generation antipsychotics have been linked to higher levels of prolactin elevation when compared to the atypical antipsychotics. It is difficult to determine whether sexual dysfunction is due to the disease or from pharmacologic therapy. More studies need to be done to better understand the relationship between these factors. Limitations of this manuscript include that it is not a systematic review or meta-analysis but the hope of the authors is that it can be a narrative guide to clinicians who are navigating this rocky terrain.

Since sexual dysfunction can impact a patient's quality of life and affect treatment adherence, it is important for physicians to be aware and monitor patients for symptoms. Strategies to combat this have focused on other pharmacologic therapies or biopsychosocial therapies. Sexual dysfunction has been treated with other drugs such as PDE inhibitors, but efficacy has been shown to be poor in those with chronic illness. The use of coping strategies may prove to be an important approach for dealing with these issues. However, more studies need to be done to show the effectiveness of this approach. Medication noncompliance remains an issue with schizophrenic patients. The side effect profile of antipsychotics can be a hinderance to consistency and may cause patients to discontinue treatment. It is important for physicians to be aware of these side effects so that they may address them.

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