Paliperidone to Treat Psychotic Disorders

Subjects: Neurosciences

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This is a comprehensive review of the literature regarding the use of paliperidone in the treatment of schizophrenia and schizoaffective disorder. It covers the background and presentation of schizophrenia and schizoaffective disorder, as well as the mechanism of action and drug information for paliperidone. It covers the existing evidence of the use of paliperidone for the treatment of schizophrenia and schizoaffective disorder.

Keywords: paliperidone palmitate ; antipsychotic agents ; psychotic disorders ; cognitive dysfunction ; dopamine ; serotonin

1. Introduction

Schizophrenia and schizoaffective disorder are two mental illnesses that have a deep impact on both their affected populations as well as our society as a whole. Multiple genetic and environmental factors contribute to the development of both disorders, leaving much of their etiology unknown [1]. The triad of schizophrenia includes cognitive impairment, positive symptoms and negative symptoms [2]. Drawing a fine line between this and schizoaffective disorder is rather difficult [3]. It is believed that schizoaffective disorder lies in the middle of the spectrum between schizophrenia and bipolar disorder, sharing characteristic symptoms of both [4]. Nonetheless, patients with either illness suffer great impairments to their everyday lives. Several studies have demonstrated that patients with schizophrenia or schizoaffective disorder experience similar social deficits in addition to a lower IQ when compared to control groups [4][5]. According to Charlson et al., “Despite being a low prevalence disorder, schizophrenia ranked the 12th most disabling disorder among 310 diseases and injuries globally” [6]. It is estimated that unemployment rates run around 80–90% in schizophrenia patients and life expectancy is decreased 14.5 years on average [2][6]. Numerous factors contribute to the early mortality rate, with one of the main causes being the higher incidence of comorbid health conditions in schizophrenia patients [6]. A second major contributing factor is the increased lifetime suicide rate, which is estimated to be around 10% in this population [7]. The only known way to decrease this risk is through compliance with treatment [7].

Although there is much undiscovered about the exact pathophysiology of these disorders, what is evident is the severe economic burden they bring to our society [2]. The estimated expense for schizophrenia in the United States in 2013 was USD 155.7 billion [8]. This included the cost for direct healthcare, direct non-healthcare (mainly unemployment and caregiving) and indirect costs [8]. Schizophrenia patients between the ages of 25 and 54 bring on the bulk of the economic burden as this age range is when individuals are typically the most economically productive [6]. Their high unemployment rate leads to serious economic losses not only from the under-productivity of the patient but additionally from the under-productivity of the family [6]. Family members frequently have to care for the patient at home and pay for treatment. This combination results in considerable deficits in the health and welfare systems [6].

2. Schizophrenia and Schizoaffective Disorder

2.1. Epidemiology

Schizophrenia and schizoaffective disorder share a very similar epidemiology, pathophysiology and presenting symptoms. However, there are some differences between them. The point prevalence of both disorders is low with schizophrenia being estimated at 0.28% and schizoaffective disorder at 0.11% [6][9]. Differences in prevalence among genders varies with studies. Some found that both schizophrenia and schizoaffective disorder had an equal distribution between sexes [6][10]. If a gender difference was found, it was trending towards schizophrenia being slightly more prevalent in males and schizoaffective disorder being slightly more prevalent in females [11][12].

Multiple studies have implicated the role of genetic abnormalities being a contributing factor for the development of schizophrenia ranging from polymorphisms in single genetic loci to copy number variants (CNVs) [1][2]. Hundreds to thousands of specific loci have been identified that are thought to contribute to the risk of developing schizophrenia [1][2].

Additionally, less frequent but high risk CNVs on genes encoding voltage-gated calcium channels, glutamate and dopamine receptors and components of post-synaptic density have been implicated as risk factors [2]. Despite the compelling evidence supporting these genetic differences in the etiopathogenesis of schizophrenia, no one single genetic variation is exclusively specific, making them non-diagnostic [1]. There is little research on the specific genetics of schizoaffective disorder. Nonetheless, based on similar heritability estimates and risk factors, it is very likely that schizoaffective disorder shares some of the genetic variants found in schizophrenia [10][12].

In addition to genetic changes, other studies have demonstrated environmental relationships. Multiple groups have found that individuals being born during the winter/early spring months are at an increased risk for developing schizophrenia [13] [14]. Individuals living in urbanized areas have also been demonstrated by multiple studies to have a considerably increased risk of developing schizophrenia and schizoaffective disorder [2][10][15]. Both of these increased risks have been proposed to possibly be the result of either in utero infection and/or other environmental exposures of the fetus [15]. Seasonal variation, as well as the high population in urban areas, could also be contributing factors to either susceptibility circumstance [15]. More recent evidence has been found to support the association between cannabis use and an increased risk of psychotic illness, including but not limited to schizophrenia and schizoaffective disorder [16][17]. A strong association with schizoaffective patients and a family history of affective disorders has also been affirmed [18].

As previously mentioned, although there are several risk factors leading to increased susceptibility of developing schizophrenia and schizoaffective disorders, no one factor is solely responsible [15]. These illnesses are highly polygenic and depend on a diverse interaction between the environment, psychology and social surroundings individual to each patient [15].

2.2. Pathophysiology

Dopamine dysregulation is one of the most widely accepted pathophysiological processes leading to the positive symptoms seen in schizophrenia [2]. The basis of this belief stems from the fact that schizophrenia patients seem to have a hypersensitivity to dopamine-like drugs, giving them enhanced symptoms such as delusions and hallucinations when compared to control groups [2][19]. This is additionally supported by evidence that current treatment with antipsychotics that block dopamine receptors sufficiently reduce hallucinations and delusions seen in these patients [1]. While it is clear that dopaminergic dysfunction plays a large role in the genesis of both schizophrenia and schizoaffective disorder, it is not the only factor responsible [20]. Abnormalities of glutamatergic function have also been implicated for contributing to the disturbances seen in these disorders [21]. Evidence from multiple studies investigating genetics, imaging, NMDA receptor (NMDAR) antagonists and treatments that increase NMDAR function in schizophrenia patients all support the notion of NMDAR hypofunction contributing to symptoms [22].

Multiple studies researching brain imaging identified that both schizophrenia and schizoaffective disorder patients had reduced grey matter volume [2][5][23]. Although these reductions were found to be more drastic in schizophrenia patients, schizoaffective patients still showed remarkable similarity with regards to having volume reductions in the same cortical areas as schizophrenia patients [5]. Both groups displayed grey matter reductions in the temporal lobe, medial frontal cortex, insula, hippocampus and cerebellum [5]. The grey matter reduction is progressive throughout the course of the illnesses, with notable activity affecting the left hemisphere and temporal lobe during the early stages [24].

2.3. Clinical Presentation

Schizophrenia and schizoaffective disorder share many of the same presenting symptoms, but they differ in their severity leading to a considerably better prognosis in schizoaffective disorder [3]. Both typically present in early adulthood and are characterized by complex psychopathology [2][6][11]. The main features of schizophrenia are positive symptoms, negative symptoms and cognitive impairment [2][25]. Positive symptoms consist of hallucinations, delusions and disorganized speech, while negative symptoms are characteristically reduced emotional expression, social withdrawal and impaired motivation [2][15]. The diminished cognitive functions experienced by patients include deficits in working memory and executive function, although there is “significant cognitive heterogeneity” among individuals [2][26].

In contrast, schizoaffective disorder is a much less stable diagnosis with much debate among clinicians and researchers [3]. According to DSM 5, schizoaffective disorder is diagnosed based on the following four criteria [27]. Criterion A states the patient must experience symptoms of psychosis from criterion A of schizophrenia simultaneously with a major mood episode (manic or depressive) [27]. Criterion B requires two or more weeks of hallucinations or delusions in the absence of a major mood episode [27]. Criterion C states symptoms of a major mood episode must be “present for the majority of the total duration of the active and residual portions of the illness” [27]. Moreover, lastly, criterion D is the acknowledgment that none of the aforementioned disturbances are a result of another condition or substance use [27]. Much of the controversy

with schizoaffective disorder is over the fact that it is described as an intermediate disorder between schizophrenia and bipolar disorder [3]. Several studies assessing cognitive functions and neuroimaging found schizoaffective disorder resembles schizophrenia significantly more than bipolar disorder [3][5][23]. IQ deficits and presenting symptoms (positive, negative and cognitive impairment) among schizophrenia and schizoaffective disorder were not different from each other but were found to be significantly different from the bipolar patients [3][5]. Additionally, brain imaging is consistent with schizoaffective disorder being more skewed towards schizophrenia than bipolar disorder [5].

3. Paliperidone Drug Info

Paliperidone is an atypical antipsychotic that is a major active metabolite of risperidone (5-hydroxyrisperidone), approved for use in the US in 2006 as daily oral extended-release tablets and 1-month or 3-month LAI formulations [28][29][30]. Paliperidone ER is indicated for treatment of schizophrenia in adults and adolescents ages 12–17 [28]. It is available in 1.5 mg, 3 mg, 6 mg, 9 mg and 12 mg [28]. The LAI form of paliperidone is indicated for the treatment of schizophrenia or schizoaffective disorder in adults as monotherapy or in conjunction with mood stabilizers, only after tolerance to oral paliperidone or risperidone has been demonstrated [29][30]. The 3-month injectable is to be used only after successful administration of the 1-month LAI [30]. The 1-month LAI is available in dosages of 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg and the 3-month injectable is available in the higher dosages of 273 mg, 410 mg, 546 mg, or 819 mg [29][30]. Contraindications to the use of paliperidone include previous hypersensitivity reactions to paliperidone or risperidone [28][29][30]. Paliperidone, like all antipsychotics, is contraindicated for use in elderly patients with dementia-related psychosis, holding a boxed warning for increased mortality in this population [28][29][30]. Adverse events of paliperidone are consistent with other atypical antipsychotics due to dopamine blockade and effects at other neurotransmitter receptors. These include cerebrovascular disease (in the elderly), neuroleptic malignant syndrome, QT prolongation, extrapyramidal symptoms, tardive dyskinesia, weight gain, dyslipidemia, hyperglycemia, hyperprolactinemia, orthostatic hypotension, leukopenia, cognitive impairment and seizures [28][29][30]. No teratogenic effects have been demonstrated, but there is increased risk for EPS and/or withdrawal symptoms in neonates exposed during pregnancy [28][29][30]. Coadministration of paliperidone ER tablets or LAI with risperidone has not been studied [28][29][30].

4. Mechanism of Action

Paliperidone is in the benzisoxazole derivative class of atypical antipsychotics (including risperidone, iloperidone and paliperidone) and acts in accordance with others in the class [28]. While the full mechanism of atypical antipsychotics is yet to be fully realized, common features of the class include affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors [31]. Unlike typical antipsychotics, atypicals, in general, have a higher ratio of antagonism at 5-HT_{2A} than D_2 receptors and have varying effects on other receptors [31]. In addition to 5-HT_{2A} and D_2 antagonism, paliperidone has antagonistic effects at α_1 and α_2 adrenergic and H_1 histaminergic receptors [32]. It has no affinity for M_1 cholinergic or β adrenergic receptors [32]. Positron emission tomography has shown paliperidone to occupy 70–80% of D_2 receptors in striatal and temporal cortex with a median effective dose of 2.38 mg/day and 2.84 mg/day, respectively [33]. Despite being the major active metabolite, paliperidone's affinity profile does not equal that of risperidone—paliperidone has a lower ratio of 5-HT_{2A}/D_2 antagonism, lower affinity for α_1 and α_2 receptors and higher affinity for H_1 receptors [34]. Paliperidone receptor antagonism has been demonstrated in rats to affect serotonergic and noradrenergic signaling differently than risperidone in vivo [35]. Additionally, molecular signaling events following receptor binding have been shown to be distinct when comparing paliperidone and risperidone [36]. Paliperidone also has been demonstrated to induce mitochondrial protein expression changes in the prefrontal cortex similar to lithium, suggesting it may have mood stabilizing properties [37]. The molecular changes observed included increased proteins associated with receptor signaling, oxidative phosphorylation, neurotransmitter release and synaptic plasticity [37].

5. Pharmacokinetics/Pharmacodynamics

Paliperidone ER is designed with an osmotically controlled-release system which allows for continuous drug delivery after oral administration and no initial titration [28]. Paliperidone itself is insoluble in water with a volume of distribution of 487 L and it has an oral bioavailability of 28% [28][31]. Paliperidone ER reaches maximal concentration (C_{max}) in 24 h and increases in C_{max} and the area under the drug concentration vs time curve (AUC) are observed after a high-fat or high-calorie meal [28][31]. Paliperidone ER demonstrates dose-response proportional AUC and C_{max} in the recommended dose range [28][31]. The time to reach steady-state is 4–5 days and terminal half-life is 23 h [28][31].

The LAI paliperidone palmitate is deposited and slowly hydrolyzed to paliperidone over time. The 1-month and 3-month injectable forms reach C_{max} in a median time of 13 days and 33 days, respectively, and both have higher C_{max} when a

deltoid injection is used rather than gluteal [29][30][31]. For this reason, the initial two doses are given in the deltoid muscle to rapidly achieve therapeutic concentration [29][30].

Paliperidone is minimally metabolized by the cytochrome P450 2D6 and cytochrome P450 3A4 enzymes; however, these are suggested to play a clinically irrelevant role overall [28][31]. Paliperidone is excreted 59% into urine unmetabolized and 11% into feces [28][31]. Divalproex sodium coadministration with paliperidone resulted in higher C_{max} and AUC of oral paliperidone [28]. Carbamazepine coadministration decreased paliperidone by increasing renal clearance of paliperidone [28]. Renal impairment resulted in decreased clearance of paliperidone by 32% in mild impairment (CrCl from 50 mL/min to <80 mL/min), 64% in moderate impairment (CrCl from 30 mL/min to <50 mL/min) and 71% in severe impairment (CrCl from 10 mL/min to <30 mL/min) [28]. Mild to moderate hepatic impairment does not alter the plasma concentration of unbound paliperidone [28]. Effects of renal or hepatic impairment have not been directly studied for the LAI paliperidone palmitate.

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