Cariprazine: Pharmacology and Clinical Management of Psychiatric Disorders

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Running title: Cariprazine in Psychiatric disorders management

Abstract

Cariprazine is a new atypical antipsychotic for schizophrenia and bipolar disorders management. In this article, the role of cariprazine, a partial D2 and D3 receptors agonist with a higher D3 affinity, in the management of psychiatric conditions is illustrated. Cariprazine caused significant improvements in psychiatric scales such as Positive and Negative Syndrome scale (PANSS), clinical global impressions (CGI) and young mania rating scales (YMRS) and was associated with side effects such as akathisia, restlessness and insomnia. These findings will guide psychiatrists and pharmacists in their clinical role for supporting psychiatric patients care.

Keywords: Cariprazine, Schizophrenia, Bipolar disorders, Pharmacology, Dopamine D3 receptor

Introduction

Psychotic disorders including schizophrenia and bipolar are severe conditions in which a person's perception, thoughts, mood and behaviour are changed [1, 2]. Schizophrenia affects 21 million people worldwide and is a leading cause of disability [3]. A diagnosis of schizophrenia is confirmed by a psychiatrist after full assessment using the International Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual (DSM-5) criteria. Schizophrenia symptoms can be divided into 'positive', such as hallucinations and delusions, and 'negative' which affect the patients' ability to function such as lack of motivation [4]. These Symptoms need to be present for a least one month before the diagnosis is made. The aetiology of schizophrenia is not fully understood, however genetic [1] with environmental factors including stress, traumatic life experiences, cannabis use could be involved [5]. 80% of schizophrenia patients could have a relapse within 5 years of recovery [6]; this risk is decreased by maintenance antipsychotics [7]. Antipsychotics provide relief from these debilitating symptoms and have been used in the treatment of bipolar disorders [8].

First generation antipsychotics such as haloperidol and chlorpromazine are dopamine (D2) receptors antagonists and could block histamine, muscarinic and alpha-1 receptors [9]. Second generation antipsychotics (SGA) are serotonin-dopamine antagonists [10]. 5HT-2A antagonism can increase dopaminergic neurotransmission in the nigrostriatal pathway, with less risk of extrapyramidal symptoms (EPS) [11]. SGA main side effects include weight gain, glucose intolerance and hyperprolactinemia [12, 13].

Cariprazine is a new atypical antipsychotic drug for the management of schizophrenia and bipolar disorder [14]. Cariprazine acts as a D2 and D3 partial agonist with a special higher affinity for D3 [15]; which differs from current

antipsychotics [10]. Cariprazine metabolism is via CYP3A4 and CYP2D6 pathways; with two clinically relevant metabolites desmethyl-cariprazine, and didesmethyl-cariprazine have similar pharmacological activity to cariprazine although didesmethyl-cariprazine has a much longer half-life (1-3 weeks), compared to cariprazine (2-4 days) [16, 17]. Cariprazine common side effects include restlessness, akathisia and insomnia [15, 16].

Cariprazine Pharmacology

Schizophrenia is associated with multi-factorial dysfunctions in glutamatergic, dopaminergic, and GABAergic neurotransmission in the central nervous system. Serotonin (5-HT) also plays a crucial role in regulating psycho-emotional, cognitive and motor functions [18, 19]. Cariprazine in a dose-dependent manner could influence acute changes in glutamate, dopamine, noradrenaline and serotonin levels [19]. Cariprazine binds Dopamine D2 and D3 receptors in a dose-dependent/saturable manner [20]. Cariprazine is a partial agonist of D2 receptor similar to aripiprazole [21] with a 10-fold higher affinity for D3 compared to D2 receptor (pKi 10, 9; respectively). Cariprazine has high affinity to 5-HT2B receptor as antagonist, moderate affinity to 5-HT1A receptor as a partial agonist and low affinity to 5-HT2A receptor as an antagonist [22]. Moreover, cariprazine displays moderate/low affinity for histamine (H1) and 5-HT2C receptors [23, 24]. Activation of D2 modulates G-protein/cAMP-dependent and Akt-GSK-3 signalling with effects on behaviours as highlighted by the activity of lithium for mania management. Cariprazine was more potent than aripiprazole as antagonist in inhibiting isoproterenol-induced cAMP and in D2R/β-arrestin 2-dependent interactions [25]. Cariprazine upregulated D2, D3 and 5-HT1A receptors levels in various brain regions, while decreased NMDA receptors [26]. Dopamine receptors differ in signal transduction, binding profile, localization and physiological

effects; with D3 involved in schizophrenia, parkinson's disease, addiction, anxiety and depression [27].

Pharmacokinetics of Cariprazine

Cariprazine has good blood brain barrier penetration with slow washout [28]. Oral bioavailability is 52% with a brain/plasma AUC ratio of 7.6:1 [29]. Cariprazine is mainly metabolised hepatically by CYP3A4 [30]. CYP2D6 mediated pathway plays a minor role in cariprazine metabolism with CYP2D6 inhibitors unlikely to have clinically relevant effects [31]. It has 2 equipotent metabolites, desmethyl and didesmethyl cariprazine [32].Cariprazine and its active didesmethyl derivative are cleared very slowly (elimination half-lives ranging from 2-5 days for cariprazine to 2-3 weeks for didesmethyl-cariprazine) [33] and steady state is reached within 1-2 weeks [16]. Cariprazine is a P-gp inhibitor in vitro, hence, the use of P-gp substrates with narrow therapeutic index such as dabigatran and digoxin require extra monitoring [31].

Cariprazine in Bipolar disorder management

Bipolar is a chronic disorder characterized by episodic recurrences of mania, depression with periods of remission [34]. Cariprazine in animal studies showed similar efficacy to lithium [25]. Several human studies showed cariprazine efficacy using Young Mania Rating Scale (YMRS) total score, YMRS single items and Clinical Global Impressions-Severity of Illness (CGI-S) score. In a trial with 497 patients, cariprazine showed superiority on all 11 YMRS single items [35]. Rates of remission and global improvement were greater for cariprazine with no decline or switch to depression [36]. Another trial confirmed cariprazine superiority in reducing YMRS and CGI-S scores with a significant percentage of patients on remission [37].

Cariprazine in Schizophrenia management

Compounds with combined 5-HT1A/D2 activities could be effective in managing a broader range of schizophrenia symptoms [38] as 5-HT1A activation leads to improved negative/cognitive symptoms with reduction of EPS induced by D2 antagonism [19, 39]. Cariprazine significantly attenuated disrupted social recognition, attention and memory [40] and caused reversal of novel object recognition impairment [41]. Cariprazine is efficacious in controlling schizophrenia symptoms and associated with a significantly longer time-to-relapse [42]. Cariprazine could also overcome deficits in cognition and social behaviour in rats [43]. In the management of negative symptoms, cariprazine showed better efficacy compared to risperidone [44] and was superior to many antipsychotics including aripiprazole [45].

Several RCT showed significant efficacy using PANSS scales (total, positive and negative) with less patients discontinuing treatment [46, 47]. CGI-S scores changes at week 6 were significant [48]. Patients with predominant negative symptoms achieved better health states and less anhedonia compared with risperidone with estimated quality-adjusted life year gain of 0.029 per patient [49, 50].

Cariprazine in the management of other psychiatric conditions

Cariprazine could be used as an adjunctive therapy in depression management. Dopamine regulation was associated with antidepressants, such as desipramine as dopaminergic dysfunction in the mesolimbic system contribute to anhedonia and psychomotor retardation and D3 expression down-regulated in depression [51]. Cariprazine attenuated anhedonic-like behaviour in mice; while reducing drinking latency (anxiolytic-like activity) [52]. Cariprazine was efficacious in reducing Montgomery-Åsberg Depression Rating Scale (MADRS) total score [53, 54].

Cariprazine showed significant changes on all PANSS hostility item especially in patients with greater baseline hostility [55]. Cariprazine could prevent relapse in human cocaine addiction and reduce cocaine rewarding effect [56].

Cariprazine tolerability

Cariprazine had low (<10%) rates of sedation, treatment discontinuation (<5%), but high akathisia rates (33%) [57] with less extrapyramidal symptoms compared to risperidone [58]. Insomnia, vomiting and headache were reported in ≥10%, while prolactin levels decreased with no significant changes in liver enzymes; mean body weight change was 1.58 kg [59]. More cariprazine patients experienced treatment-emergent akathisia (cariprazine: 22%; placebo: 6%) or extrapyramidal symptoms (cariprazine: 16%; placebo: 1%) [37]. Akathisia, extrapyramidal and diastolic blood pressure symptoms showed a dose-response relationship. There were significant changes in fasting glucose levels (~ 7mg/dl compared to just 1.7 mg/dl for placebo). No clinical changes in electrocardiogram parameters or high QTC>500ms were observed [17]. A multi-center clinical trial showed no unexpected safety issues/deaths [60]. Restlessness, nausea, dyspepsia, tremor, back pain were common (incidence≥5%) [61]. Somnolence is common as cariprazine is considered an activating medication (NNH=65 - Low somnolence risk) [62, 63]. Cariprazine similar to haloperidol and aripiprazole affects 7-dehydrocholesterol (7-DHC) conversion to cholesterol [64].

Discussion

This review investigated cariprazine efficacy and safety for psychiatric conditions management. Cariprazine is taken once daily (1.5 -12mg) without regard to food. The dose should be adjusted in patients who receive CYP450 inhibitors, is contra-indicated for patients with severe hepatic or renal disease [65]. Cariprazine is a D3 and

D2 receptor partial agonist with higher selectivity for D3 expressed mainly in brain areas associated with motivation and reward-related behaviour [66].

In Schizophrenia, cariprazine resulted in significant improvement in PANSS total and improved negative symptoms compared to other antipsychotics such as risperidone. Cariprazine showed significant improvements in CGI-S and shifted from the extremely/severely ill to mildly ill/better category [67]. In Bipolar disorders, cariprazine resulted in significant improvements in YMRS and was efficacious as monotherapy - improved remission rates (OR: 2.08) [68] and is recommended alone or in combination as first-line treatments for acute mania [69]. There was significant higher risk of EPS [70] with a low risk of discontinuing [67]. Clinical trials results need to be interpreted with caution as treatment length was short in the majority of the studies (3-6 weeks) with several doses used and no clear evidence for long-term effects.

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