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Short-term efficacy and tolerability of lurasidone in the treatment of acute schizophrenia: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Lurasidone, an azapirone derivative, is a novel second generation antipsychotic with potent binding affinity for dopamine D2, serotonin 5-HT_{2A}, 5-HT_{7}, 5-HT_{1A}, and noradrenaline $alpha_{2C}$ receptors. This updated meta-analysis of randomized controlled trials (RCTs) examined the short-term efficacy and tolerability of lurasidone in the treatment of acute schizophrenia.

Methods: Double-blinded RCTs reporting on the short-term effects of lurasidone were included. Standardized mean difference (SMD) with their 95% confidence interval (CI), and number needed to harm (NNH) were computed.

Results: The meta-analysis had 8 RCTs with 16 active arms that included 2373 patients with acute schizophrenia who were randomized to either lurasidone (20–160 mg/day; n = 1570) or placebo (n = 803) groups. Lurasidone was superior to placebo with regard to change in total psychopathology [SMD: -0.34, (95%CI: -0.48, -0.20), P < 0.00001], positive symptoms [SMD: -0.47, (95%CI: -0.57, -0.36), P < 0.00001], negative symptoms [SMD:-0.34, (95%CI: -0.45, -0.22), P < 0.00001], and general psychopathology [SMD: -0.36, (95%CI: -0.48, -0.24), P < 0.00001]. Results were consistent for total psychopathology in 11 out of the 13 subgroups. Lurasidone resulted in higher weight gain [SMD: 0.15, (95% CI: 0.06, 0.24), P = 0.001] and BMI [SMD: 0.17, (95%CI: 0.07, 0.28), P = 0.002] than placebo, but the differences were not clinically significant. Lurasidone group had less frequent inefficacy (NNH = 14) and discontinuation due to any reason (NNH = 17), but was associated with more frequent vomiting, akathisia, dystonia, parkinsonism, somnolence, dizziness, sedation, nausea, and weight gain of ≥7% of the initial weight (NNH = 11–50).

Conclusion: This meta-analysis of 8 short-term studies supported the efficacy and safety of lurasidone in the acute phase of schizophrenia, particularly at the higher dose range of 80 mg/day.

1. Introduction

Schizophrenia is a severe chronic major mental disorder, affecting approximately 1% of the population worldwide (Van and Kapur, 2009). It is characterized by abnormalities in the area of perception, mood, cognition, and behavior (Wang et al., 2013) impairing patients' social and vocational functioning (Saha et al., 2005). Antipsychotic medications are the mainstay treatment for schizophrenia with second generation antipsychotics being associated with more favorable adverse effect profile in terms of extrapyramidal symptoms compared to first generation antipsychotics (Leucht et al., 2009a). However, most second generation antipsychotics also induce metabolic dysfunctions, such as diabetes, atherogenic dyslipidemia (Solmi et al., 2016; Vancampfort et al., 2015), cardiovascular disease (CVD) and increase CVD-related mortality (Correll et al., 2017).

Lurasidone, an azapirone derivative, is a novel second generation antipsychotic developed by the Dainippon Sumitomo Pharma research laboratories in Japan (Pompili et al., 2018). Lurasidone has potent

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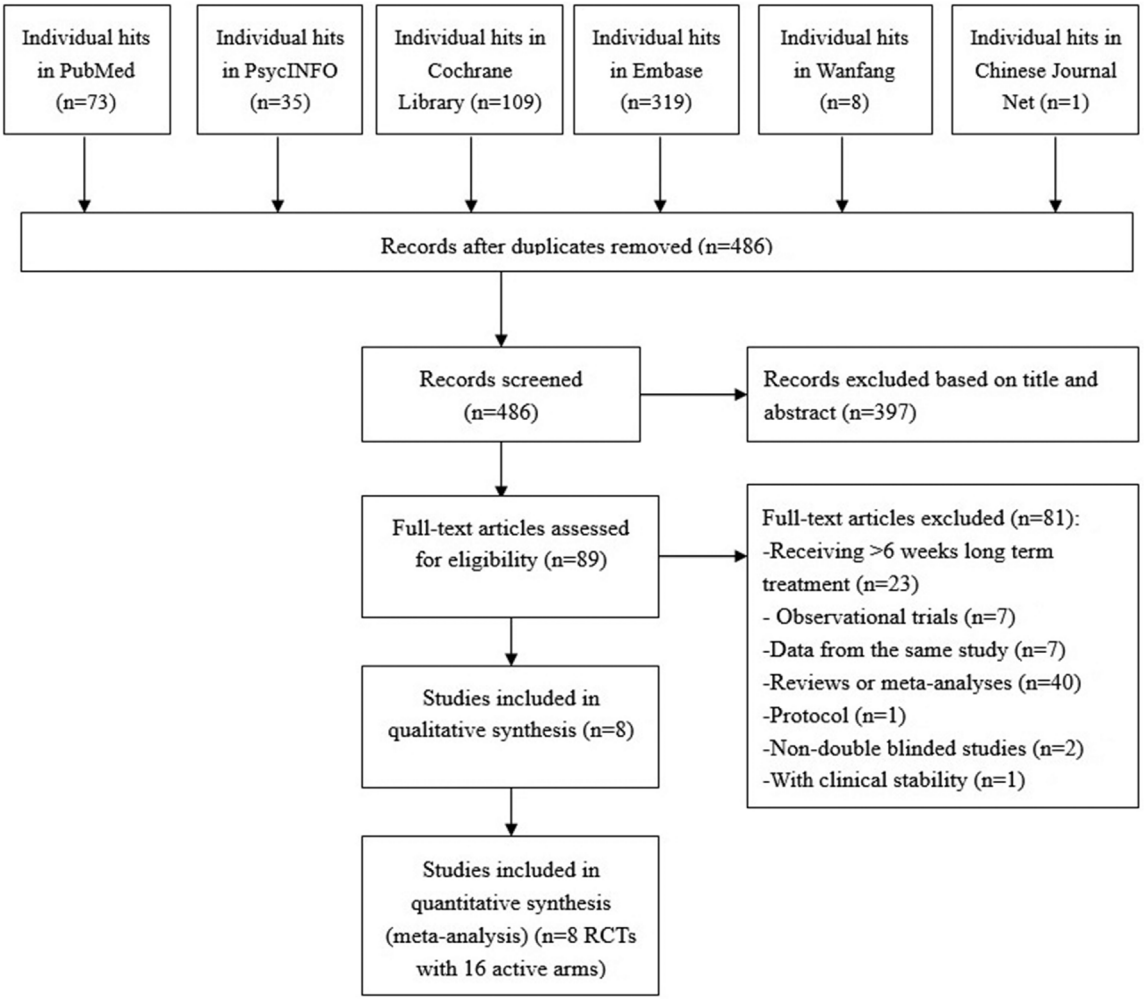

Fig. 1. PRISMA flow diagram.

binding affinity for dopamine D2, serotonin 5-HT_{2A}, 5-HT_{7}, 5-HT_{1A}, and noradrenaline alpha$_{2C}$ receptors (Ishibashi et al., 2010). Although its efficacy and safety in treating in mania has not been established, lurasidone has been approved for the treatment of adolescents (13–17 years; 40–80 mg/day) and adults (40–160 mg/day) with schizophrenia in the USA, Canada, Australia, and Europe, as well as for the treatment of adolescents (10–17 years; 40–80 mg/day as monotherapy) and adults (20–120 mg/day as monotherapy and adjunctive therapy with lithium or valproate) with depressive episodes in bipolar I disorder in the USA and Canada (Latuda Prescribing Information, 2012).

Compared to many second generation antipsychotics, lurasidone has negligible affinity for histamine H1 receptors and muscarinic M1 receptors (Ishibashi et al., 2010), both of which are thought to be responsible for weight gain, increased plasma lipid levels and impaired glucose metabolism caused by second generation antipsychotics (Citrome and Volavka, 2005). Several randomized controlled trials (RCTs) (e.g. Loebel et al., 2013; Meltzer et al., 2011; Nakamura et al., 2009; Ogasa et al., 2013) found that lurasidone did not result in clinically relevant adverse drug reactions (ADRs) in terms of metabolic and electrocardiographic (ECG) parameters. Further, lurasidone also has low propensity for extrapyramidal symptoms. However, the findings of published RCTs (Goldman et al., 2017; Loebel et al., 2013, 2016; Meltzer et al., 2011; Nakamura et al., 2009; Nasrallah et al., 2013; Ogasa et al., 2013; Potkin and Kimura, 2015) that examined the short-term efficacy and tolerability of lurasidone for acute schizophrenia have not been consistent.

A recent pooled analysis (Loebel et al., 2015) of 5 short-term RCTs (Loebel et al., 2013; Meltzer et al., 2011; Nakamura et al., 2009; Nasrallah et al., 2013; Ogasa et al., 2013) of lurasidone in acute schizophrenia found that compared to placebo, lurasidone significantly improved the Positive and Negative Syndrome Scale (PANSS) total and all factor scores. However, this pooled analysis did not include salient outcome measures, such as discontinuation rate and ADRs. Two meta-analyses (De Hert et al., 2012; Zhang et al., 2017) on antipsychotic-induced metabolic effects concluded that lurasidone had the lowest risk of weight gain and glucose changes compared to other antipsychotics. Furthermore, several RCTs of lurasidone in schizophrenia (Goldman et al., 2017; Loebel et al., 2016; Potkin and Kimura, 2015) have been recently published that were not included in previous meta-analyses (De Hert et al., 2012; Loebel et al., 2015).

Thus, we conducted this updated meta-analysis of RCTs to evaluate the short-term efficacy and tolerability of lurasidone in the treatment of acute phase of schizophrenia. We hypothesized that compared to placebo, lurasidone would be effective and safe in treating psychotic symptoms in the acute stage of schizophrenia.

2. Methods

2.1. Literature search strategy

Two researchers (WZ and D-BC) independently carried out the literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Moher et al., 2009). They searched both English (PubMed, PsycINFO,