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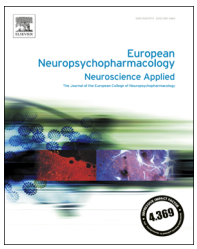

REVIEW

Pharmacogenetics of clozapine response and induced weight gain: A comprehensive review and meta-analysis

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Abstract
Clozapine (CLZ) is the prototype atypical antipsychotic and it has many advantages over other antipsychotic drugs. Several data suggest that both CLZ response and induced weight gain are strongly determined by genetic variability. However, results remain mainly inconclusive. We aim to review the literature data about pharmacogenetics studies on CLZ efficacy, focusing on pharmacodynamic genes. Further, we performed meta-analyses on response when at least three studies for each polymorphism were available. Sensitivity analyses were conducted on Caucasian population when feasible. Electronic literature search was performed to identify pertinent studies published until May 2014 using PubMed, ISI Web of Knowledge and PsycINFO databases. For meta-analyses, data were entered and analyzed through RevMan version 5.2 using a random-effect model.
Our literature search yielded 9266 articles on CLZ; among these, we identified 59 pertinent pharmacogenetic studies. Genotype data were retrieved for 14 polymorphisms in 9 genes. Among these, we had available data from at least three independent samples for 8 SNPs in 6 genes to perform meta-analyses: DRD2 rs1799732, DRD3 rs6280, HTR2A rs6313, rs6311, rs6314, HTR2C rs6318, HTR3A rs1062613, TNFa rs1800629. Although literature review provided conflicting results, in meta-analyses three genetic variants within serotonin genes resulted associated to CLZ response: rs6313 and rs6314 within HTR2A gene and rs1062613 within HT3A

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gene. On the other hand, no clear finding emerged for CLZ-induced weight gain. Our results suggest a possible serotonergic modulation of CLZ clinical response.

1. Introduction

Clozapine (CLZ) is the prototype atypical antipsychotic which was introduced in the early 1970s. It has many advantages over other antipsychotic drugs. It acts on both positive and negative symptoms as well as on cognitive deficits associated with schizophrenia and it has superior efficacy and tolerability compared with typical analogs (Leucht et al., 2013). So, CLZ is one of the most efficacious antipsychotics. However, it was withdrawn shortly afterwards its introduction in clinical practice for safety concerns, in particular for its link with potentially fatal agranulocytosis.

CLZ has been also associated with weight gain. For example, the cumulative proportions of patients gaining 10%, 15% or 20% of their baseline weight during the first 12 weeks of CLZ treatment have been reported to be 55%, 18% and 12%, respectively (Umbricht et al., 1994). Consistently, in a study of 16 weeks of CLZ treatment, 38% of the patients experienced marked weight gain (Leadbetter et al., 1992). The mechanisms underlying CLZ-induced metabolic side effects remain unclear. Antipsychotic weight gain could be due to caloric intake rather than reduced thermogenesis. The mechanisms underlying antipsychotic induced weight gain may involve several different peptide, neurotransmitter and receptor systems in the appetite and reward systems in the brain, including antihistaminergic effects, histamine H1 receptors, activation of hypothalamic adenosine monophosphate-activated protein kinase (AMPK), modulation of hormonal signaling of ghrelin and leptin, changes in the production of tumor necrosis factor-alpha (TNF)-alpha, adipokines, serotonin 5-HT2A, 5-HT2C and 5-HT6 receptors, a1-, a2- and b3-adrenergic receptors, muscarinic M3 receptors, melanocortin 4 receptor (Malhotra et al., 2012) and dopamine D1, D2 and D3 receptors. Clozapine and olanzapine may also impair glucose metabolism by blockade of the muscarinic M3 receptor (Roerig et al., 2011). Subjects with schizophrenia taking CLZ showed adiponectin plasma levels significantly lower than controls (Bartoli et al., 2015). The large individual variability in weight gain due to CLZ treatment suggests a genetic role in the determination of this side effect. Many genes have been studied in association with antipsychotic induced weight gain: the most consistently replicated findings are in the melanocortin 4 receptor (MC4R), the serotonin 2C receptor (HTR2C), the leptin, the neuropeptide Y (NPY) and the cannabinoid receptor 1 (CNR1) genes (for a complete picture of the field see Shams and Müller, 2014).

In 1989, after CLZ has been shown to be effective in treatment-resistant schizophrenia, the United States Food and Drug Administration (FDA) approved its use solely for treatment resistant schizophrenia, requiring strict hematological monitoring with regular white blood cell and absolute neutrophil counts. In 2002, CLZ was also approved for the treatment of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder (FDA).

In the last decades, FDA published other five black box warnings for CLZ treatment (particularly for agranulocytosis, seizures, myocarditis, for “other adverse cardiovascular and respiratory effects", and for "increased mortality in elderly patients with dementia-related psychosis”).

Thus, although about 30% of patients with schizophrenia are treatment resistant and 10% had survived a serious suicide attempt, suggesting that at least 35–40% should be treated with CLZ, only 4.4% had been treated with CLZ in the clinical practice (Meltzer, 2012).

Furthermore, even if CLZ has shown efficacy in treatment-resistant schizophrenia, only 30–60% of treatment-resistant schizophrenic patients respond to CLZ, showing a great individual variability. Taking into account these data, several studies have been performed in order to identify predictors of CLZ response. Clinically, both the presence of an extrapyramidal syndrome with previous antipsychotics and a diagnosis of paranoid schizophrenia were found to be predictors of good response, whereas early age at onset of illness and female gender were associated with poor response (Lieberman et al., 1994). Nonetheless, these clinical predictors were still not sufficient to provide useful indication for clinical practice. Thus, the detection of stronger predictors could be important in order to identify patients who will have substantial benefits from CLZ treatment, allowing this potentially dangerous treatment to be limited.

Some data suggest that both CLZ response and induced weight gain are strongly determined by genetic variability (Theisen et al., 2005; Vojvoda et al., 1996; Wehmeier et al., 2005). Thus, the investigation of genetic variants modulating CLZ effectiveness may allow to detect CLZ responders before the treatment itself.

Several studies have been performed with this aim on CLZ, unfortunately with controversial results, similarly to other antipsychotics (Zhang and Malhotra, 2013). Nonetheless, for CLZ this aim is even more hard to achieve since CLZ displays one of the most complex pharmacological profile among available drugs, acting on several neuronal systems at different levels (Wenthur and Lindsley, 2013). In particular, compared to other antipsychotics, CLZ exhibits a lower activity for the D2 receptor (DRD2) and higher affinity to D3 receptors (DRD3). In addition, CLZ was found to have a 10 times higher affinity to D4 dopamine receptor (DRD4) compared to its affinity for DRD2 and DRD3, suggesting DRD4 as its primary target, though specific DRD4 compounds were not successful. Further, CLZ has relatively high affinity for some serotonin receptor subtypes. It is a serotonin receptor blocker with high affinity for the 2A (HTR2A), 2C (HTR2C), 3A (HTR3A), 6 (HTR6) and 7 (HTR7) receptors (Meltzer, 1994). Finally, CLZ acts also on other receptors, such as the histamine H1, adrenergic and glutamatergic receptors. All these molecular effects may be implicated, at least partially, in the determination of its effectiveness.