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Adjunctive minocycline for schizophrenia: A meta-analysis of randomized controlled trials

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Abstract
This study aimed to conduct a meta-analysis of the efficacy and safety of adjunctive minocycline for schizophrenia. Randomized controlled trials (RCTs) comparing adjunctive minocycline with placebo in patients with schizophrenia were included in the meta-analysis. Two independent investigators extracted and synthesized data. Standard mean differences (SMDs), risk ratio (RR) ±95% confidence intervals (CIs) and the number-needed-to-harm (NNH) were calculated. Eight RCTs with 548 schizophrenia patient including 286 (52.2%) patients on minocycline (171.9±31.2 mg/day) and 262 (47.8%) on placebo completed 18.5±13.4 weeks of treatment. Meta-analyses of Positive and Negative Syndrome Scale (PANSS) (7 RCTs with

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8 treatment arms)/Brief Psychiatric Rating Scale (BPRS) (1 RCT) total score [SMD: −0.64, (95% CI: −1.02, −0.27), P=0.0008; I^2=74%], positive, negative and general symptom scores [SMD: −0.69 to −0.22 (95%CI: −0.98, −0.03), P=0.02-0.00001; I^2=7-63%] revealed a significant superiority of adjunctive minocycline treatment over the placebo. There was no significant difference regarding neurocognitive function, discontinuation rate and adverse drug reactions between the two groups. This meta-analysis showed that adjunctive minocycline appears to be efficacious and safe for schizophrenia. Due to significant heterogeneity, future studies with a large sample size are needed to confirm these findings.

1. Introduction

As a severe psychiatric disorder, schizophrenia affects approximately 1% of the population worldwide (Kelly et al., 2015) and is associated with impaired social and cognitive functions and lowered quality of life (Ogino et al., 2011; Tomida et al., 2010, 2011). Although the etiology of schizophrenia is still unclear, some studies (Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010) indicated that schizophrenia patients with severe negative symptom and poor cognitive function may result from neuroinflammation by activating microglia and hypofunction of glutamate and/or dysfunction of N-methyl-D-aspartate (NMDA)-type glutamate receptors. In addition, NMDA receptor antagonists could lead to psychotic symptoms and cognitive impairments in healthy persons and exacerbate psychotic symptoms in patients with schizophrenia (Krystal et al., 1994).

Several anti-inflammatory medications, such as minocycline, cyclooxygenase (COX) inhibitors, anti-TNF alpha and polyunsaturated fatty acids (PUFAs), have shown certain antipsychotic effects (Fond et al., 2014). Of them, minocycline is a semi-synthetic second-generation tetracycline with anti-inflammatory and brain-protective actions (Levkovitz et al., 2010; Liu et al., 2014) and could inhibit activated microglia (Kim et al., 2004) and enhance glutamate neurotransmitters (Chaves et al., 2009). The potential antipsychotic and neuroprotective effects of minocycline have been demonstrated in animal models (Levkovitz et al., 2007; Zhang et al., 2007). Several case series (Kelly et al., 2011; Miyaoka et al., 2007) and open-label trials (Miyaoka et al., 2008) have found that minocycline is an effective and safe adjunctive treatment for schizophrenia. In contrast, however, the results of randomized controlled trials (RCTs) (Chaudhry et al., 2012; Ghanizadeh et al., 2014; Kelly et al., 2015; Khodaie-Ardakani et al., 2014; Levkovitz et al., 2010; Liu et al., 2014; Zeng, 2015; Zhang, 2015) regarding the efficacy and safety of adjunctive minocycline for schizophrenia have been mixed.

A recent meta-analysis (4 RCTs, n=330 participants) (Oya et al., 2014) and a review (Fond et al., 2014) supported the superiority of adjunctive minocycline over placebo in schizophrenia. However, both of them did not include non-English databases. In addition, several recent RCTs were not included.

We conducted this meta-analysis of RCT and systematically assessed the efficacy and safety of adjunctive minocycline for schizophrenia.

2. Experimental procedures

2.1. Search strategy and selection criteria

Both Chinese and English databases were included because the former is not widely known to the international readership. Two independent investigators systematically searched PubMed, PsycINFO, Embase, Cochrane Library databases and the Cochrane Controlled Trials Register, CJN, WanFang and CBM databases from inception of the databases until January 7, 2016 using the following search terms: (minocyline OR minocycline) AND (Schizophrenic Disorder OR Disorder, Schizophrenic OR Schizophrenic Disorders OR Schizophrenia OR Dementia Praecox). There were no restrictions regarding sample size and study period. Additional eligible studies were also sought by scrutiny of the reference lists of the retrieved articles and relevant review articles.

According to *PICOS* acronym, we used the following selection criteria: Participants (*P*): patients with schizophrenia by any diagnostic criteria. Intervention (*I*): minocycline plus antipsychotics (APs). Comparison (*C*): APs plus placebo or APs monotherapy. Outcomes (*O*): efficacy and safety. Study design (*S*): RCT. Case series, non-randomized studies, and non-original research (reviews and meta-analyses) were excluded.

2.2. Data extraction and outcome measures

Data extraction was based on intent to treat (ITT) analysis or modified ITT data (i.e., at least one dose or at least one follow-up assessment) if provided; two independent investigators conducted data synthesis and assessment of study quality. Inconsistencies were resolved by consensus or involvement of a third reviewer.

The primary outcome measure was the endpoint symptomatic improvement assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The key secondary outcomes were as follows: positive, negative and general psychopathology subscales of the PANSS or the BPRS or the total scores of the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and/or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), neurocognitive function assessed by the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008), the Global Assessment of Function (GAF) scale (Endicott et al., 1976) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005), Calgary Depression Rating Scale (CDRS) (Addington et al., 1994), the Clinical Global Impression (CGI) scale (Haro et al., 2003), discontinuation rate and adverse drug reactions (ADRs).