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Adjunctive metformin for antipsychotic-induced hyperprolactinemia: A systematic review

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ABSTRACT

This systematic review examines adjunctive metformin therapy for the treatment of antipsychotic-induced hyperprolactinemia. A computerized search of databases in Chinese and the international databases in English provided three trials with a total of 325 patients including one randomized clinical trial (RCT) and two observational studies (single-group, before-after design). A meta-analysis could not be conducted. The quality of evidence ranged from "very low" to "moderate". Metformin patients had a significant decrease in serum prolactin level with a mean of 54.6 μg/l in the three trials. In the RCT, menstruation restarted in 67% of those with menstrual disturbances versus 5% in placebo. In one observational study, 91% of patients no longer had signs or symptoms of galactorrhea. In the RCT, adverse drug reactions (ADRs) occurred at similar incidence rates among metformin and placebo patients, except that no significant increases in nausea, insomnia and agitation occurred which were not associated with discontinuations. Our systematic review indicated that adjunctive metformin significantly lowered prolactin level and relieved prolactin-related symptoms in patients with antipsychotic-induced hyperprolactinemia. Future higher quality RCTs need to verify the currently available limited evidence based on three trials which suggest that adjunctive metformin may be used effectively and safely for antipsychotic-induced hyperprolactinemia.

1. Introduction

Use of antipsychotic drugs has been associated with hyperprolactinemia, defined as a prolactin level above the reference interval; this hormonal abnormality can interfere with the functioning of metabolic, endocrine, and reproductive systems (Inder and Castle, 2011). Hyperprolactinemia is one of the most common antipsychotic-induced adverse drug reactions (ADRs), with respective rates in male and female patients of 18–76% and 42–90% (Bushe and Shaw, 2007; Byerly et al., 2007; Bushe et al., 2008; Kim et al., 2012). Hyperprolactinemia has short- and long-term consequences that can seriously affect quality of life: menstrual irregularities, amenorrhea, galactorrhea, sexual dysfunction, gynecomastia, infertility, decreased bone mineral density, even breast cancer, and poor treatment adherence (Halbreich and Kahn, 2003; O'Keane, 2008; Bushe et al., 2009; Kishimoto et al., 2012).

Several strategies have been recommended to prevent or alleviate hyperprolactinemia (Bostwick et al., 2009; Nunes et al., 2012). Using the lowest effective antipsychotic dose can minimize hyperprolactinemia risk, but maintenance treatments with reduced doses have higher relapse rates than the full treatment dose (Wang et al., 2010). Switching to an antipsychotic agent with lower hyperprolactinemia risk is not always possible since the alternative agent may not be effective or may be associated with other ADRs (Leucht et al., 2013). Adding a dopamine agonist, such as bromocriptine, amantadine or cabergoline, can compromise antipsychotic efficacy and aggravate abnormal involuntary movements (Marken et al., 1992; Biller et al., 1999; Yuan et al., 2008). Some studies indicate that some herbal medicines can resolve risperidone-induced hyperprolactinemia (Yamada et al., 1999; Yuan et al., 2008). Adding aripiprazole can be effective for hyperprolactinemia (Shim et al., 2007; Hoffer et al., 2009; Kane et al., 2009; Li et al., 2013), but antipsychotic polytherapy is not

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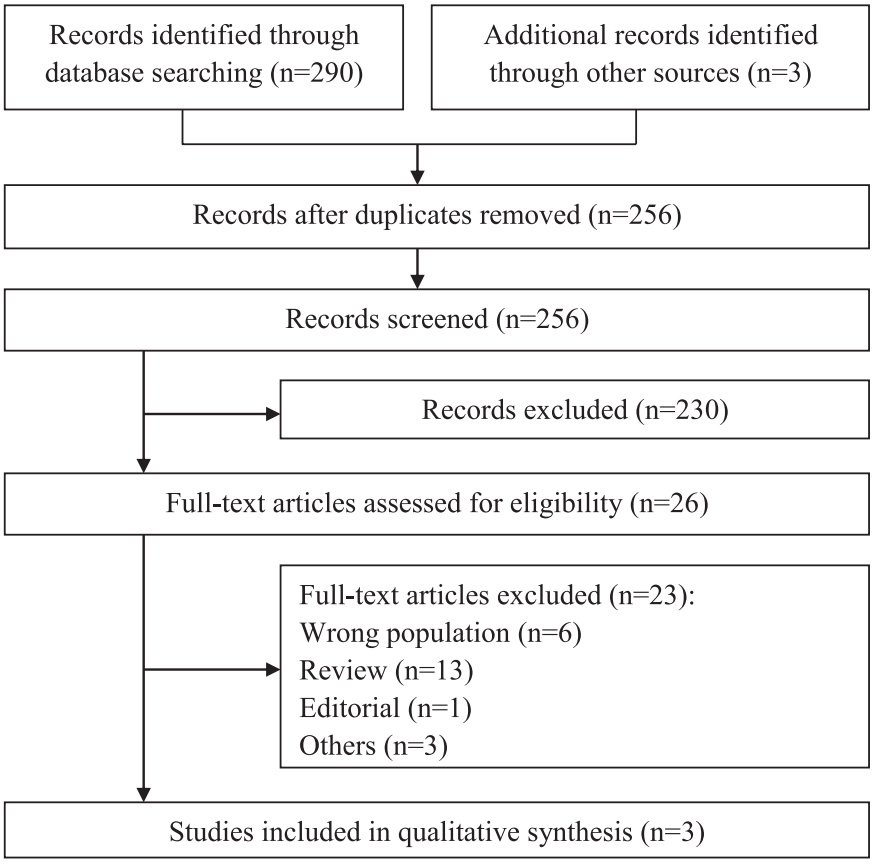

Fig. 1. Flow diagram of study selection.

recommended (Lehman et al., 2004), and can increase other ADRs (Bhattacharjee and El-Sayeh, 2008).

Metformin is the most prescribed oral antidiabetic drug for the treatment of type 2 diabetes mellitus, and has been reported to reduce prolactin levels (Velazquez et al., 1994; Billa et al., 2009; Krysiak et al., 2015). It is possible that reducing prolactin levels may also contribute to decreased weight, since Baptista et al. (2001) proposed that prolactin may be involved in antipsychotic-induced weight gain. They found a positive association between prolactin levels and body mass index (BMI) only in males. According to them, several mechanisms may explain this association, since prolactin may: (1) impair the synthesis of the gonadal sex hormones which may influence brain hormones and promote obesity; (2) interfere with synthesis of brain peptides and secondarily with opioid-endorphin rewarding aspects of feeding; (3) induce hyperinsulinemia promoting fat deposit; and (4) stimulate feeding by acting directly at the hypothalamus.

The role of metformin on antipsychotic-induced hyperprolactinemia has recently been brought to psychiatrists' attention (Smith, 2012). There have been a few trials of the addition of metformin for hyperprolactinemia (Liang, 2013; Shi and Ding, 2013), and a randomized controlled trial (RCT) indicated normalization in prolactin levels and patients' recovery from prolactin-related symptoms (Wu et al., 2012).

As there has been no thorough systematic review on this topic, the aim of this systematic review was to evaluate adjunctive metformin therapy for the treatment of antipsychotic-induced hyperprolactinemia, particularly focusing on efficacy and safety.

2. Methods

2.1. Protocol

Before we conducted this systematic review, our protocol of reviewing metformin use for antipsychotic-induced hyperprolactinemia was published online (http://www.crd.york.ac.uk/prospero/); the registration number was CRD42014013839 at the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PRISMA provides an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (Moher et al., 2009).

2.2. Types of trials

All types of adult trials evaluating the efficacy and safety of adjunctive metformin for antipsychotic-induced hyperprolactinemia were eligible for inclusion. We included studies with well-defined treatment protocols and which reported at least one of the outcome measures mentioned below. We included case series, RCTs, open-label retrospective studies and prospective trials. We excluded meta-analyses and systematic reviews.

2.3. Outcome measures

We recorded clinical outcomes according to intent-to-treat (ITT) analyses where available. The primary outcome measures of this systematic review were efficacy of treatment (serum prolactin level and prolactin-related symptoms: oligomenorrhea, amenorrhea, and galactorrhea recovery) and ADRs (nausea, extrapyramidal symptoms, insomnia and agitation, somnolence, headache, and dry mouth), as reported in the studies. The secondary