



# Metformin to reduce weight gain and metabolic disturbance in schizophrenia

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**ABSTRACT FROM:** Mizuno Y, Suzuki T, Nakagawa A, *et al.* Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull* 2014;40:1385–403.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Weight gain and metabolic disturbances (ie, obesity and diabetes) are common side effects of second-generation antipsychotics.<sup>1</sup> Pharmacological interventions might be one approach to preventing or reducing these adverse events in individuals with schizophrenia. Since an earlier Cochrane review in 2007 we conducted,<sup>2</sup> research has doubled from 18 to 40 randomised controlled trials representing 19 unique interventions and an updated review of the evidence was timely.

## METHODS OF THE STUDY

Mizuno and colleagues performed a systematic review and meta-analyses of pharmacological interventions to mitigate weight gain and metabolic disturbances in schizophrenia. EMBASE, MEDLINE, PsycINFO, PubMed, and the Cochrane Library were searched until November 2013 and references of relevant papers were hand searched. Unpublished studies were searched in clinical trial registries (<http://clinicaltrials.gov/>). Studies met inclusion if: (1) they were double-blind randomised placebo controlled trials using an adjunct medication to reduce antipsychotic-induced metabolic disturbances, (2) the majority of participants had a diagnosis of schizophrenia or related psychotic disorder and (3) metabolic changes were reported as the primary outcome. Forty-one published trials, eight unpublished, and one article in press were included in final analyses. For continuous outcomes, mean differences were calculated using the inverse variance statistical method and random-effects model in adjusting for study heterogeneity. Study heterogeneity was assessed using the  $I^2$  statistic, and publication bias was assessed with funnel plots. The primary outcome was change in body weight.

## WHAT DOES THIS PAPER ADD

- ▶ This systematic review adds further evidence that metformin is a safe pharmacological adjunct for counteracting antipsychotic-related weight gain. Overall, there was a mean difference of  $-3.17$  kg (95% CI  $-4.44$  to  $-1.90$ ) in studies compared to placebo (see below for further details).
- ▶ Pooled effects for other pharmacological adjuncts were also significant but effects were smaller. Other adjuncts remain understudied in comparison to metformin.
- ▶ There was some indication that interventions in general are more effective for first-episode patients. There was a mean difference of  $-3.52$  kg (95% CI  $-4.93$  to  $-2.11$ ) in 10 first-episode trials. In comparison, the mean difference was  $-1.71$  kg (95% CI  $-2.43$  to  $0.00$ ) in 30 non-first-episode trials.

## LIMITATIONS

- ▶ This is a rigorous systematic review that follows the PRISMA statement for reporting. There are no methodological concerns with the conduct of the review.
- ▶ In terms of existing research, the sample sizes and numbers of studies for most types of pharmacological adjuncts were limited, and long-term effects beyond 24 weeks have not been examined.

## WHAT NEXT IN RESEARCH

- ▶ Research is required in examining the long-term effects of using pharmacological adjuncts for weight gain. The mean duration of studies was approximately 12 weeks and there is no evidence of longer term benefit at this stage as most studies have only examined outcomes after 12 weeks.
- ▶ Research should also examine how to combine pharmacological interventions with lifestyle interventions (diet and physical activity) and whether the combination is associated with greater effects.

## DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

This review confirms that metformin can be used for modest weight loss among individuals with schizophrenia. We agree with the authors' acknowledgement that pharmacological approaches to weight gain in schizophrenia should be considered only after behavioural interventions have been tried or switching antipsychotics is not feasible. An initial focus on a behavioural approach is important for several reasons. First, it is in line with current evidence-based guidelines for the treatment of obesity, which calls first for multicomponent (diet and physical activity) behavioural intervention.<sup>3</sup> Second, irrespective of weight loss, clinicians should keep in mind that small, sustained positive changes in physical activity and dietary intake are associated with significant health benefit. Indeed, fitness may be more important than overweight or obesity for cardiovascular risk.<sup>4</sup> Such interventions are feasible although they will likely need to be highly structured, with early and intensive support initially and offering reduced but continued support over time (if not indefinitely).<sup>5</sup> For some individuals with schizophrenia, however, behavioural interventions may not be appropriate due to significant impairment in functioning and insight. Accordingly, consideration is also required to the settings in which many individuals with schizophrenia may reside (eg, hospital settings; shared housing) and to modifying the environment to promote habitual physical activity and reduce energy intake.

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**Competing interests** None declared.

doi:10.1136/eb-2014-102039

Received 2 February 2015; Revised 18 April 2015; Accepted 28 May 2015

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