Title: Can metformin undo weight gain induced by antipsychotics? *J Fam Pract*. 2008;57:526-530.	
Potential PURL Review Form: Randomized Controlled Trials	
SECTION1: IDENTIFYING INFORMATION	
1.0 Citation	Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, He YQ, Liu YJ, Chen JD, Li LH. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA.* 2008;299:185-193.
1.1 Editors classification of nominated study	Potential PURL Review Date: 3/13/08
1.2 Editors reason for classification	None given
1.4 Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3051&itool=AbstractPlus-def&uid=18182600&db=pubmed&url=http://jama.ama-assn.org/cgi/pmidlookup?view=long&pmid=18182600
1.5 First date published study available to readers	1/9/08
1.6 PubMed ID	18182600
1.7 Nominated By	Sarah-Anne Schumann
1.8 Institutional Affiliation of Nominator	University of Chicago
1.9 Date Nominated	2/14/08
1.10 Identified Through	*JAMA*
1.11 PURLS Editor	Bernard Ewigman
1.12 Nomination Decision Date	2/14/08
1.13 Potential PURL Review Form (PPRF) type	Randomized controlled trials
1.14 Other comments, materials or discussion	
1.15 Assigned Potential PURL Reviewer	Sarah-Anne Schumann
1.16 Reviewer Affiliation	University of Chicago
1.17 Date Review Due	3/13/08

1.18 Abstract	CONTEXT: Weight gain, a common adverse effect of antipsychotic medications, is associated with medical comorbidities in psychiatric patients. OBJECTIVE: To test the efficacy of lifestyle intervention and metformin alone and in combination for antipsychotic-induced weight gain and abnormalities in insulin sensitivity. DESIGN, SETTING, AND PATIENTS: A randomized controlled trial (October 2004-December 2006) involving 128 adult patients with schizophrenia in the Mental Health Institute of the Second Xiangya Hospital, Central South University, China. Participants who gained more than 10% of their predrug weight were assigned to 1 of 4 treatment groups. INTERVENTIONS: Patients continued their antipsychotic medication and were randomly assigned to 12 weeks of placebo, 750 mg/d of metformin alone, 750 mg/d of metformin and lifestyle intervention, or lifestyle intervention only. MAIN OUTCOME MEASURES: Body mass index, waist circumference, insulin levels, and insulin resistance index. RESULTS: All 128 first-episode schizophrenia patients maintained relatively stable psychiatric improvement. The lifestyle-plus-metformin group had mean decreases in body mass index (BMI) of 1.8 (95% confidence interval [CI], 1.3-2.3), insulin resistance index of 3.6 (95% CI, 2.7-4.5), and waist circumference of 2.0 cm (95% CI, 1.5-2.4 cm). The metformin-alone group had mean decreases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 3.5 (95% CI, 2.7-4.4), and waist circumference of 1.3 cm (95% CI, 1.1-1.5 cm). The lifestyle-plus-placebo group had mean decreases in BMI of 0.5 (95% CI, 0.3-0.8) and insulin resistance index of 1.0 (95% CI, 0.5-1.5). However, the placebo group had mean increases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 0.4 (95% CI, 0.1-0.7), and waist circumference of 2.2 cm (95% CI, 1.7-2.8 cm). The lifestyle-plus-metformin treatment was significantly superior to metformin alone and to lifestyle plus placebo for weight, BMI, and waist circumference reduction. CONCLUSIONS: Lifestyle intervention and metformin alone and in combination demonstrated efficacy for antipsychotic-induced weight gain. Lifestyle intervention plus metformin showed the best effect on weight loss. Metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone. Trial Registration clinicaltrials.gov Identifier: NCT00451399.

SECTION 2: DETAILED STUDY DESCRIPTION	
2.1 Number of patients starting each arm of the study?	128 patients, 32 in each group
2.2 Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	INCLUSIONS: Age 18-45 (mean age 26, 50%-50% men-women) with first psychotic episode of schizophrenia, >10% weight gain from predrug body weight within first year of tx with antipsychotic (clozapine, olanzapine, risperidone or sulpiride), on only 1 antipsychotic, relatively stable improvement; under care of parent or other adult caregiver who monitored and recorded food

<table>
<tr><td></td><td>intake, exercise, meds; mean baseline BMI 24.5; EXCLUSIONS: liver or renal dysfunction, cardiovascular disease, diabetes mellitus, pregnancy, limitations to physical activity, other psych diagnosis, substance abuse</td></tr>
<tr><td>2.3 Intervention(s) being investigated?</td><td>12 weeks of metformin (750 mg/d) alone, placebo alone, lifestyle intervention + placebo, or lifestyle intervention + metformin; lifestyle intervention included psychoeducational program focused on role of eating and activity in wt management; administered 4 times (baseline, 4, 8, & 12 weeks); dietary intervention-AHA step 2 diet: <30% fat, 55% carbs, >15% protein, >15 g fiber, reviewed 3 day food diaries with dietician at follow up visits; exercise: start with walk or jog 30 min 7 days per week at 70% heart rate reserve (week 1 with exercise physiologist, then home-based-light-to-moderate exercise with follow-up treadmill tests for adherence and also exercise and HR records)</td></tr>
<tr><td>2.4 Comparison treatment(s), placebo, or nothing?</td><td>Treatments (metformin with or without lifestyle intervention) vs placebo</td></tr>
<tr><td>2.5 Length of follow up? Note specified end points e.g. death, cure, etc.</td><td>12 weeks</td></tr>
<tr><td>2.6 What outcome measures are used? List all that assess effectiveness.</td><td>Primary: weight changes, BMI, waist circumference, fasting glucose, fasting insulin, insulin resistance index (IRI); secondary=Positive and Negative Symptom Scale (PANSS) score and adverse effects</td></tr>
<tr><td>2.7 What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.</td><td>See Table 2 for treatment outcomes (p. 190)
Difference between baseline and endpoints: details and P values with each comparison Table 3, p. 191
<table>
<tr><td></td><td>Lifestyle + metformin</td><td>Metformin</td><td>Lifestyle</td><td>Placebo</td></tr>
<tr><td>Weight, kg</td><td>-4.7 (-5.7 to -3.4)</td><td>-3.2</td><td>-1.4</td><td>3.1</td></tr>
<tr><td>BMI, kg/m^2</td><td>-1.8</td><td>-1.2</td><td>-0.5</td><td>1.2</td></tr>
<tr><td>Waist circumference, cm</td><td>-2.0</td><td>-1.3</td><td>0.1</td><td>2.2</td></tr>
<tr><td>Fasting glucose, mg/dL</td><td>-7.2</td><td>-10.8</td><td>-7.2</td><td>1.8</td></tr>
<tr><td>IRI</td><td>-3.6</td><td>-3.5</td><td>-1.0</td><td>0.4</td></tr>
</table>
IRI, insulin resistance index.</td></tr>
<tr><td colspan="2">SECTION 3: INTERNAL VALIDITY</td></tr>
<tr><td>3.1 Study addresses an appropriate and clearly focused question</td><td>Well addressed</td></tr>
<tr><td>3.2 Random allocation to comparison groups</td><td>Well addressed</td></tr>
</table>

3.3 Concealed allocation to comparison groups	Well addressed
3.4 Subjects and investigators kept "blind" to comparison group allocation	Well addressed
3.5 Comparison groups are similar at the start of the trial	Well addressed
3.6 Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Well addressed
3.7 Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well addressed
3.8 Are patient oriented outcomes included? If yes, what are they?	Decrease in BMI-patient oriented if patient cares about weight
3.9 What percent dropped out, and were lost to follow up? Could this bias the results? How?	118/128 completed 12 weeks of treatment (7.8% dropped out)
3.10 Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes
3.11 If a multi-site study, are results comparable for all sites?	N/A
3.12 Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	No-Ministry of Science and Technology of People's Republic of China

SECTION 4: EXTERNAL VALIDITY	
4.1 To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Patients on atypical antipsychotics with >10% weight gain in first year of treatment who are at risk of developing diabetes
4.2 In what care settings might the findings apply, or not apply?	Psychiatry, primary care, endocrine
4.3 To which clinicians or policy makers might the findings be relevant?	Psychiatrists, primary care doctors
SECTION 5: REVIEW OF SECONDARY LITERATURE	
5.1 DynaMed excerpts	Includes this study already
5.2 DynaMed citation/access date	Antipsychotics (general information) Updated 2008 Feb 11; accessed 2.12.2008
5.3 UpToDate excerpts	Mentions Baptista article that found metformin did not work and also the 2006 *Am J Psychiatry* study that found metformin works in kids on antipsychotics
5.4 UpToDate citation/access date	Accessed 2.12.08; updated 9.21.07; Jibson MD, "Overview of antipsychotic medications"
5.5 PEPID PCP excerpts	None
5.6 PEPID citation/access data	
5.7 Other excerpts (USPSTF; other guidelines; etc.)	
5.8 Citations for other excerpts	
SECTION 6: CONCLUSIONS	
6.1 How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1

6.2 If 6.1 was coded as 4 or above, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
6.3 Are the results of this study relevant to the health care needs of patients cared for by "full scope" family physicians, general internists, general pediatricians, or general ob/gyns? Are they applicable without significant change in programs or policies such as the organization or financing of practice? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	2
6.4 Please explain your response to item 6.3.	This study is relevant to patients in primary care practices, many of whom take antipsychotic medications and are at risk for weight gain and related complications. While the antipsychotics are usually prescribed by psychiatrists, the primary care providers should monitor patients for side effects of antipsychotics and treat patients accordingly; no changes in programs or policies required
6.5 What is the main recommendation for change in practice, if any? Include a description of the change in practice, the indications, and the target population.	In patients on atypical antipsychotics with weight gain of >10% initial body weight, a combination of lifestyle intervention and metformin can decrease wt gain and risk of diabetes; this was a short study-only 12 weeks; it would be nice to see a study that follows patients for a longer period of time to see if this intervention continues to prevent weight gain, diabetes, and complications of diabetes in the long term; also patients had adult caregiver which may promote better adherence to treatment than patients living independently
SECTION 7: EDITORIAL DECISIONS	
7.1 FPIN PURLs editorial decision (select one)	Pending PURL—Forward to JFP Editor for interest in JFP publication as a PURL
7.2 FPIN PURLS Editor	Bernard Ewigman
7.3 Date of decision	March 13, 2008
7.4 Brief summary of decision	This is a well-done RCT of use of metformin and lifestyle interventions for schizophrenic patients started on an antipsychotic agent who have significant weight gain. Metformin plus lifestyle vs

	placebo showed almost an 8-kg favorable difference after 12 weeks. Metformin alone vs placebo = 6.3-kg difference. Fasting glucose and insulin resistance were also improved. We think this is a useful solution to the common problem of weight gain among patients taking antipsychotic agents. This solution may also prevent the onset of diabetes, though this study was not designed to address that issue.