The Zivin et al. study has other methodological problems. The authors collapsed categories of a comorbidity index into one continuous covariate, altering magnitudes of comorbidity and increasing the possibility of data misinterpretation (3). Their study does not address whether particularly elevated risk exists in individuals with specific comorbid illnesses (e.g., heart failure)—those individuals targeted in the FDA warning. In addition, the person-time measure used by the authors permits more than one observation for the same individual during periods when different dosages were prescribed. In this situation, the possible group effects generated between different individuals and within the same individual in regression analyses should be examined; otherwise, the precision of regression estimates is compromised. Finally, contrary to the FDA warning, the authors concluded that no increase in risk of ventricular arrhythmia was associated with high-dosage citalopram treatment without providing the theoretical explanation for their finding. Their results suggested that high-dosage antidepressants decreased the risk, although they avoided coming to that conclusion. Further study is needed to unravel the biological mechanisms underlying that finding.

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Adequate Dosing for Second-Generation Antipsychotics in Establishing Treatment Resistance in Schizophrenia

TO THE EDITOR: Treatment resistance in schizophrenia requires evidence of two previous failed antipsychotic trials of 6 weeks at a dose of 600 mg in chlorpromazine equivalents (1), while the original criteria for clozapine's role in treatment resistance stipulated a dose of 1,000 mg in chlorpromazine equivalents (2).

Second-generation antipsychotics have largely supplanted their first-generation counterparts in the last decade, and studies have attempted to derive chlorpromazine equivalents for these agents either through expert consensus or calculation methods. This calls into question the impact of these different approaches on studies employing chlorpromazine equivalents.

The estimated doses of five commonly prescribed second-generation antipsychotics, using four widely used methods, are listed in Table 1. Immediately apparent is the wide variation in calculated doses for any given second-generation antipsychotics; for example, at 600 mg of chlorpromazine equivalents, doses of risperidone vary between 6 mg and 12 mg and doses of aripiprazole vary between 24 mg and 45 mg. These differences are amplified at 1,000 mg of chlorpromazine equivalents.

At 1,000 mg of chlorpromazine equivalents, calculated doses for the second-generation antipsychotics uniformly exceed the maximum dosages currently recommended for these agents (3). Even at 600 mg of chlorpromazine equivalents, values frequently lie outside the recommended dosage range. As importantly, the calculated doses differ markedly based on the method employed.

This variance raises practical considerations, for example, in declaring a failed second-generation antipsychotics trial in the process of defining treatment-resistant schizophrenia. The wide variation challenges the validity of using chlorpromazine equivalents to compare across antipsychotics. The reported near-maximal effective dose of chlorpromazine was 400–450 mg, not 600–1,000 mg, and there appears to be little evidence to support high doses in treatment-resistant schizophrenia (4). In addition, the high doses calculated raise serious safety concerns and fly in the face of regulatory dosing recommendations. Accordingly, adopting chlorpromazine equivalents may not be appropriate for evaluating an adequate dosage for specific second-generation antipsychotics, and we suggest that a more appropriate means to confirm a failed clinical trial is suboptimal response at the maximum recommended dosage range for a specific second-generation antipsychotics, as per product monograph.

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TABLE 1. Computed Doses of Antipsychotics at 600 and 1,000 mg Chlorpromazine Equivalents From Consensus and Calculation Methods

Drug (mg)	600 mg Chlorpromazine Equivalents				1,000 mg Chlorpromazine Equivalents				Dosing		
	Consensus		Calculation		Consensus		Calculation		Highest Dose		Recommended Range[a]
	Kane[b]	Gardner[c]	Woods[d]	Andreasen[e]	Kane[b]	Gardner[c]	Woods[d]	Andreasen[e]	Kane[b]	Gardner[f]	
Risperidone	6.6	6	12	7.9	11.7	10.0	20.0	13.2	10.5	8.5 (1.0)	2–8
Olanzapine	24.0	20	30	28.5	33.3	33.3	50.1	47.5	40.0	30 (0)	10–20
Quetiapine	720.0	750	450	852.0	1,000.0	1,250.0	751.5	1,420.0	950.0	1,000 (162)	300–750
Ziprasidone	168.0	160	360	303.0	200.0	266.7	601.2	505.0	180.0	200 (40)	80–160
Aripiprazole	24.0	30	45	38.5	33.3	50.0	75.2	64.2	30.0	30 (0)	10–30
Haloperidol	12.0	10	12	11.0	22.2	16.7	20.0	18.4	25.0	20 (4.0)	6–20

[a] Recommended dose range for treatment of an acute episode (3).
[b] Doses obtained and approximated from haloperidol, 10 mg for 600 mg of chlorpromazine equivalents and 20 mg for 1,000 mg of chlorpromazine equivalents, from guideline 5A of Kane et al. (4).
[c] Doses computed from dose equivalency ratio versus chlorpromazine (5).
[d] Doses calculated from table provided in Woods (6).
[e] Doses calculated from power transformation for chlorpromazine equivalent (7).
[f] Median (interquartile range) maximum doses (5).

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Metformin and Alzheimer's Disease Risk

TO THE EDITOR: In the September issue of the *Journal*, Jarskog et al. (1) report and Correll et al. (2) discuss a 4-month trial of metformin that concluded "metformin was modestly effective in reducing … risk factors for cardiovascular disease" and "represents a safe … option for patients who are motivated to lose weight." That study spanned 4 months, but the treatment of cardiovascular risk factors may continue indefinitely. Imfeld et al. (3) reported that long-term metformin use (over 60 prescriptions or more than 7 years) but not use of other antidiabetic medications such as sulfonylureas, thiazolidinediones, or insulin was associated with a small increased risk of developing Alzheimer's disease (adjusted odds ratio, 1.71).

I would be grateful if Jarskog et al. and Correll et al. would compare the benefit they anticipate from reducing cardiovascular risk factors with metformin in psychiatric, nondiabetic patients to the risk of increased Alzheimer's disease from metformin.

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Response to Rosenfeld

TO THE EDITOR: We appreciate Dr. Rosenfeld bringing attention to a recent report by Imfeld et al. (1) suggesting that long-term metformin use may increase the risk for Alzheimer's disease in elderly patients with diabetes mellitus. In fact, a number of clinical and preclinical reports within the past 5