ment. Anything having to do with blinding (including open label designations) relates to protecting knowledge of treatment allocations after assignment.

Allocation concealment is frequently confused with blinding. Unfortunately, in this instance, that semantic confusion may have contributed to inaccurate assessment of the impact of allocation concealment vis-a-vis sequence generation and blinding. Admittedly, assessing the quality of randomized trials embodies many difficulties. Nevertheless, comparing results across methodological studies necessitates the most accurate measurements and analyses that are available.

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In Reply: Dr Liberati and colleagues and Dr Sánchez García point out an error in the "Results" section of our article. The data in Table 2 are based on our initial analyses, which we revised during the review process. We apologize for the confusion. The correct data are presented in the TABLE. The chosen cutoff for low- and high-quality studies is, of course, arbitrary, but the data in the Table clearly show that there was no reason for choosing a cutoff point on a post hoc basis. In contrast to the opinion of Liberati et al, we think that SDD studies are very appropriate to explore the relationship between study quality and observed effects. As opposed to mortality, the end point of pneumonia is rather weak since establishing this diagnosis is extremely difficult. Therefore, this end point is prone to investigator bias, which is consistent with our findings. At no point did we claim that only RCTs were included.

We also agree with Sánchez García that the results of our study and those of other recent meta-analyses with regard to the effects of SDD on mortality deserve attention. But we do not agree with him or with Liberati et al that the results of a meta-analysis should be used to prove a hypothesis. Our data and those of other meta-analyses suggest that there might be a survival benefit when using SDD, which should be demonstrated in a prospective, randomized, and preferably double-blind study. We are aware of the polarized opinions about the potential benefits and risks of SDD. The aim of our study was to analyze the effects of study quality on study outcome. Only in the final paragraph of the discussion did we briefly and—in our opinion—objectively summarize the existing controversies on SDD.

We thank Drs Graf and Janssens for their additional analysis on the lack of relationship between study quality and the IF of the journal in which the study was published. We can add that in additional analyses we also could not find a relationship between the outcome of the study and the journal's IF. So, with regard to efficacy of SDD, there is no evidence for a positive or negative publication bias.

We agree with Drs Schultz and Cates that the term "open label" for the method of allocation concealment may have been confusing. However, we did not use this term for unmasked administration of medication. In fact, with "open label" we categorized those studies that used a method of concealment of allocation that did not fulfill stringent and clear criteria. The majority of articles failed to report the method of concealment of allocation. Nondefined concealment might have been a more appropriate term.

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Table. Relative Risk Reductions for Pneumonia and Mortality in Studies Categorized as "Low" and "High" Quality, Based on Different Cutoff Points for the Methodological Quality Score*

"Low" Quality Studies			"High" Quality Studies		
Cutoff Point	No. of Studies	RRR (95% CI)	Cutoff Point	No. of Studies	RRR (95% CI)
Pneumonia					
≤6	9	0.79 (0.65-0.94)	>6	21	0.5 (0.40-0.59)
≤7	11	0.79 (0.67-0.91)	>7	19	0.46 (0.35-0.56)
≤8	14	0.69 (0.58-0.80)	>8	16	0.45 (0.34-0.56)
Mortality					
≤4	7	0.15 (−0.05-0.35)	>4	24	0.11 (0.01-0.21)
≤5	12	0.17 (0.03-0.32)	>5	19	0.09 (−0.02-0.19)
≤6	15	0.13 (0.01-0.25)	>6	16	0.10 (−0.02-0.23)

*RRR indicates relative risk reduction; CI, confidence interval.

Atypical Antipsychotic Drugs and Hyperglycemia in Adolescents

To the Editor: Hyperglycemia has been associated with the atypical antipsychotic agents clozapine and olanzapine,[1] and a recent case report described diabetic ketoacidosis associated with olanzapine in a pediatric patient.[2] To gain further insight into the association between hyperglycemia and these 2 drugs in the pediatric population, we queried the US Food and Drug

Administration (FDA) MedWatch drug surveillance system to identify cases occurring in patients younger than 19 years.

Olanzapine-Associated Cases. Between January 1996 and May 2001, the FDA received 9 spontaneous-adverse-event reports of hyperglycemia in adolescents who were aged 13 to 18 years (4 males and 5 females) and received olanzapine in daily doses of 10 to 20 mg. Seven presented with newly diagnosed hyperglycemia and 2 had exacerbation of preexisting diabetes. Presentation occurred within 1 week of drug initiation for 2 patients and within 6 months for 6 others. Glycemic control improved in 4 patients after olanzapine was discontinued or the dose decreased. In 1 patient, however, hyperglycemia recurred in the absence of islet cell antibodies 6 months after the patient switched to risperidone and venlafaxine.[2] The most common concomitant drugs included benztropine, sertraline, tegretol, and valproate. In this group, there was 1 death from necrotizing pancreatitis.

Clozapine-Associated Cases. Between January 1993 and March 2001, the FDA received 11 reports of hyperglycemia in adolescents who were aged 13 to 18 years (7 males and 4 females) and received clozapine in daily doses from 100 to 1000 mg.[1] Eight had newly diagnosed hyperglyecemia, 2 experienced exacerbation of preexisting diabetes, and the diabetes status of 1 was unknown. Presentation occurred within 6 weeks of drug initiation for 5 patients and within 6 months for 5 others. Clozapine was discontinued or the dose decreased in 6 patients. Three experienced improved glycemic control. One patient presented with profound hyperglyemia (1300 mg/dL) and pancreatitis with elevated lipase levels 34 days after clozapine treatment was initiated. Clonazepam was the sole concomitant medication.

Comment. Diabetes is relatively uncommon in children. The National Health Assessment and Nutrition Survey found less than 1 incident case per 1000 yearly for the population aged 0 to 24 years.[3] A 1983 study found an incidence rate of 13.5 per 100,000 yearly for those younger than 20 years.[4] Crude estimates of exposure to atypical antipsychotics can be calculated according to the total numbers of US prescriptions, mean prescription length, and fraction of patients aged 0 to 18 years through 2000, yielding approximately 4200 patient-years for clozapine and 97000 patient-years for olanzapine.[5,6] Assuming no underreporting, these data suggest that the risk for hyperglycemia with clozapine is approximately 10-fold higher than background. The incidence of hyperglycemia with olanzapine appears similar to the background rate, assuming that all cases were reported to the FDA. Given that underreporting is typical of these voluntary adverse-event systems, the number of cases may be larger. The mechanism for hyperglycemia remains unknown.

Among these 20 patients, 2 also had pancreatitis, which suggests a causal association with the antipsychotic agents. Pancreatitis is uncommon in children in the absence of trauma, anatomic anomalies, heritable metabolic disorders, and exposure to toxins or drugs.[7] Although valproate has been associated with pancreatitis,[8] only 1 patient of the 2 patients in our series had been treated with this drug. These 2 cases of pancreatitis were identified by our search for hyperglycemia and so may not represent all cases of pancreatitis.

Atypical antipsychotic agents continue to have a role in treating pediatric psychotic disorders, although they are not currently labeled for pediatric use. Until systematic studies of the various agents are conducted to determine relative and absolute risk, physicians should consider monitoring patients for hyperglycemia.

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