

caused by the addition of a second antibody may have reduced the availability of oxaliplatin and thus may explain the negative outcome of our trial involving patients receiving chemotherapy plus bevacizumab and cetuximab. Although we did not measure drug concentrations, the similar incidence of neurotoxicity, a common side effect of oxaliplatin, between the two treatment groups does not support this hypothesis. However, it may be worthwhile to further investigate this idea.

Fрати and Codacci-Pisanelli comment on the percentages of patients who received second-line treatment and patients who had received previous adjuvant treatment. First, these two factors are unlikely to have had any effect on the primary outcome of our study. Second, possible explanations are that patients with persistent neurotoxic effects after previous oxaliplatin-based adjuvant treatment were excluded from our study, and that the national Dutch guidelines on colorectal cancer do not routinely advocate adjuvant treatment in patients with stage III rectal cancer. Finally, the number of patients receiving second-line treatment may appear low because the definition of second-line treatment in our trial, unlike that used in many other trials, did not include the reintroduction of first-line treatment after a drug holiday; this narrower definition was also used in our previous trial.¹ Even so, the percentages of patients who had received previous adjuvant treatment and patients who received second-line treatment in our trial do not differ substantially from the percent-

ages in many other trials with similar patient populations.

EGFR expression was not an inclusion variable in our study, since EGFR expression detected by immunohistochemical analysis was previously shown not to correlate with response to cetuximab treatment.² Our trial was not designed to detect survival differences in relation to EGFR expression.

Copur et al. address the effects of sex and *EGFR* polymorphisms. Few data are available on the effect of sex on treatment with targeted agents in colorectal cancer. In a study of cetuximab monotherapy as compared with best supportive care, no such effect was observed.³ We are currently investigating the role of several germ-line polymorphisms and of *BRAF* mutation status, as suggested by Loupakis et al.

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Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

TO THE EDITOR: Ray et al. (Jan. 15 issue)¹ report that both typical and atypical antipsychotic drugs were associated with a doubling of the risk of sudden cardiac death, a risk that was dose-dependent and untested for time dependence. The authors state that the likely mechanism of action is an increase in the risk of serious ventricular arrhythmias, although they acknowledge that other mechanisms may be involved. Increased mortality among the severely mentally ill is well known, and although the illnesses themselves are associated with increased mortality,²⁻⁴ their undertreatment may lead to even higher mortality.⁵ An increased risk of cardiac events may be due to the illnesses themselves and associated risk factors or to their treat-

ment, since chronic psychotic disorders are strongly associated with cardiac risk factors, including poor nutrition, obesity, substance abuse, smoking, lack of exercise, poverty, and stress. Moreover, doses of antipsychotic drugs are often higher in patients with more severe illness.

In their study, Ray et al. matched users and nonusers of antipsychotic drugs according to age, sex, timing of treatment exposures, cardiovascular risk scores, and other measures in order to avoid confounding. Nevertheless, patients who received antipsychotic drugs had an increase by a factor of 5.0 in indexes of psychiatric illness and an increase by a factor of 3.5 in exposure to other psychotropic drugs. Prudence requires that we pay close atten-

tion to the findings of this study in balancing the risks and benefits of antipsychotic drugs. However, the reported rates of death appear to be of uncertain clinical significance and require study in patients who are matched for psychiatric morbidity.

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TO THE EDITOR: In documenting the cardiovascular risks associated with the use of antipsychotic drugs, Ray et al. provide important information to assist the clinician in making an informed assessment of the risks and benefits of these drugs. In their analysis of specific drugs, however, it is surprising that the authors did not present data on the atypical agents ziprasidone and aripiprazole. Concern about the potential cardiac arrhythmogenicity of ziprasidone was raised even before its approval by the Food and Drug Administration.¹ In addition, the identification of ziprasidone and aripiprazole as agents that are less likely to have adverse metabolic effects (obesity, hyperglycemia, and dyslipidemia²) than other atypical antipsychotic drugs has led some clinicians to view them as safer and therefore to prefer them. The presentation of data on these agents would substantially enhance the usefulness of this report.

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THE AUTHORS REPLY: Baldessarini's description of our results as "untested for time dependence" overlooks the analysis that was restricted to the first 365 days of use of antipsychotic drugs, which had findings similar to those in the primary analysis. He also raises the issue of confounding according to antipsychotic indication, which was considered extensively in our report. An important analysis was that of the cohort that excluded patients with a baseline diagnosis of schizophrenia or related psychoses. Control subjects were matched according to a propensity score, which is one method of matching patients for psychiatric morbidity. In this cohort, both users and nonusers of antipsychotic drugs had similar distributions of baseline psychiatric medications, diagnoses, and health care utilization. Findings were very similar to those in the primary cohort. The absence of increased risk among former users of antipsychotic drugs and the marked dose-response relationship for current users provide further evidence that confounding according to indication did not explain our findings.

As noted by Baldessarini, many studies have reported excess mortality among patients with schizophrenia. Given our findings and those of clinical trials¹ involving the elderly, which have shown an increase in the rate of death from any cause among users of antipsychotic drugs, one wonders to what extent the excess mortality among patients with schizophrenia reflects the effects of the drugs with which this disease is nearly always treated.

We concur with Price that drug-specific data regarding ziprasidone and aripiprazole would be of interest. To ensure adequate power for individual drug analyses, we had an a priori requirement of at least 3000 person-years of current use, which would provide an expected five cases of sudden cardiac death under the null hypothesis. Neither ziprasidone nor aripiprazole met this criterion. However, both of these drugs were included in the analysis of all atypical antipsychotic drugs. On the basis of the principle that findings for the entire study population should apply to subgroups unless there is convincing evidence to the contrary,² we believe that these particular atypical

antipsychotic drugs should not be considered free of risk for sudden cardiac death until further data become available.

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Decontamination of the Digestive Tract in ICU Patients

TO THE EDITOR: De Smet and colleagues (Jan. 1 issue)¹ do not address the effects of selective digestive tract decontamination (SDD) in intensive care units (ICUs) on the increasing prevalence of enterococci, which leads to additional use of vancomycin and the emergence of vancomycin-resistant enterococci (VRE). The authors report that in the short term, rates of antibiotic-resistant gram-negative bacteria during SDD or selective oropharyngeal decontamination (SOD) were lower than during standard care. Rates of bacteremia with enterococci were slightly lower during SDD or SOD. However, no data on carriage of enterococci are presented.

In the United States and Europe, the rapid emergence of VRE was preceded by the emergence of ampicillin-resistant *Enterococcus faecium* (AREF).² After starting to use SDD in our hospital, as part of the trial reported by de Smet et al., we observed a sharp increase in the prevalence of AREF. After the trial was completed, the prevalence of AREF remained high, and the first serious VRE epidemic in our hospital occurred, involving 30 patients. Eight clinical wards were involved, including four ICUs; one ward was closed for several weeks. Before introducing SOD or SDD in ICUs, decision makers should take into account the possible emergence and amplification of resistant enterococci, especially in low-prevalence settings.

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TO THE EDITOR: In their trial of SDD and SOD, de Smet et al. report significant reductions in rates of death and ICU-acquired bacteremia at 28 days. A likely mechanism for this benefit is a reduction in ventilator-associated pneumonia,^{1,2} which is associated with a doubling in the rate of death among ICU patients.³ However, the authors do not provide data on rates of ventilator-associated pneumonia or the use of recommended preventive practices, such as semirecumbent positioning, daily cessation of sedation infusions, and spontaneous-breathing trials, which are frequently combined as part of an evidence-based “ventilator bundle.”⁴ If these preventive measures had been used for all patients, the absolute benefit of SDD or SOD in this trial might have been greatly reduced, making these interventions much less attractive, given their associated cost, requirement for additional nursing labor, and potential for antibiotic resistance. These details regarding rates of ventilator-associated pneumonia and the use of preventive measures are also important for understanding the generalizability of these results to ICUs, which have adopted routine use of ventilator bundles.

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