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In Reply:—Johnstone and Martinec point out once again the need for cost-benefit studies in medicine. In the 1990s, this will become more important as the federal government attempts, through legislative and other means, to curb the ever rising health-care costs plaguing our economy. It is not appropriate, however, to insist that every clinical trial be conducted as a cost-benefit study. Changes in the way medicine is practiced, regardless of the specialty or subspecialty in question, occur as a result of collection, publication, and analysis of many kinds of scientific data. Many questions must be answered before a new therapy or intervention can supplant older, previously established practices. In addition to cost-effectiveness, questions of safety and efficacy are of primary concern. Our recent multicenter study of ondansetron as a possible treatment for postoperative nausea and vomiting[1] sought to answer some of these questions. Earlier single-center studies[2,3] indicated that ondansetron appeared effective, when compared to placebo, as a treatment for postoperative nausea and vomiting. The dosages of ondansetron used in these and other earlier studies were based on the clinical experience compiled during the studies of ondansetron as an antiemetic for chemotherapy-induced emesis. Our study was designed to determine whether doses smaller than 8 mg would be effective in treating postoperative nausea and vomiting. In addition, we evaluated the safety of ondansetron in our study population (*i.e.,* patients undergoing outpatient surgery). At the time of our study, ondansetron was not approved by the Food and Drug Administration for the indication in question. This study was conducted as part of the approval process. Since the drug was not approved as a treatment for postoperative nausea and vomiting when our study was conducted, no pricing or packaging information applicable to this indication was available.

If ondansetron is to become part of the accepted treatment of postoperative nausea and vomiting, further studies comparing it to other accepted treatments should be performed. These studies should include data necessary to make appropriate cost-benefit analyses. This will not be as easy as it sounds. Pharmacoeconomic studies must define in specific dollar amounts not only the cost of the intervention but a quantifiable benefit. Though cost of a drug appears to be straightforward, one must remember that, as noted by Johnstone and Martinec, the cost to the patient differs from the wholesale cost to the hospital. Various fees are associated with dispensing and administering medications, often resulting in a cost to the patient many times greater than the hospital's cost of the drug. Consequently, generic medications can result in substantial patient cost, even when the hospital cost may be trivial. It may be more difficult to quantitate benefit. Some measures of benefit lend themselves to simple analysis (*e.g.,* increased or decreased recovery room stay, time lost from work, unanticipated hospitalization). Other measures may be difficult to assess. For instance, some complications associated with postoperative nausea and vomiting may occur infrequently but have serious or even catastrophic results when they do occur (*e.g.,* bleeding under a flap graft, evisceration of ocular contents after an open eye procedure). It becomes difficult to attach precise dollar figures to quality-of-life issues such as the psychologic impact on the patient of prolonged postoperative nausea and vomiting. Indeed, though data from pharmacoeconomic and quality-of-life studies should be included as part of the decision-making process when considering changes to customary practices, they should not be the primary focus during initial safety and efficacy studies.

It is imperative, however, that every practicing physician be aware of the patient cost of the tests and therapies before they are ordered. Finding the most economic approaches to patient care is the responsibility of every health-care professional. It should be an integral part of each institution's quality-improvement process. It is not acceptable medical practice to prescribe medications, order therapies, or perform laboratory tests without a knowledge of the cost *versus* the presumed benefit.

Our study was designed to answer specific questions about the potential suitability of ondansetron as a treatment for postoperative nausea and vomiting. Our aim was to present data on the safety, efficacy, and dose of ondansetron when used as a treatment for postoperative nausea and vomiting. The study was not designed to determine whether ondansetron is superior in efficacy or cost-effectiveness to other available treatments. Further studies are needed to answer these and other questions.

Phillip E. Scuderi, M.D.
Bernard Wetchler, M.D.
Department of Anesthesia
The Bowman Gray School of Medicine
Wake Forest University
Medical Center Boulevard
Winston-Salem, North Carolina 27157-1009

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In Reply:—We agree with Johnstone and Martinec that it would be highly desirable for anesthesia studies involving new drugs to include a cost evaluation.[1] Unfortunately, information on the cost of new drugs is not available at the time phase 3 studies are conducted.[2–4] Given the high cost of drug development (variously estimated at $150–250 million), it is not surprising that new drugs, such as ketorolac and ondansetron, are more expensive than the drugs they are replacing.

Determining the cost of a new therapeutic agent is a complex process because consideration must be given to direct and indirect costs (table 1). We also agree with Johnstone and Martinec that the inclusion of drug-company employees as coauthors may raise concerns regarding the objectivity of the authors' presentation of favorable data. However, the inclusion of drug-company employees as coauthors did not prevent Wong *et al.* from concluding that the use of ketorolac (as an alternative to the opioid analgesics) was not associated with a difference in the overall "quality of life" or the time to resumption of normal activities.[2] These authors suggested that the lack of a global "outcome difference" between ketorolac and opioid analgesics needs to be weighed against the cost differential between ketorolac and the standard analgesic drugs. Other recently published studies[5–7] suggested that ketorolac offers only minor advantages over fentanyl in the ambulatory setting. Nevertheless, patients at risk for opioid-related side effects (*e.g.*, respiratory depression, nausea, vomiting, ileus, pruritis) may benefit from the use of nonsteroidal antiinflammatory drugs, such as ketorolac.

The drug cost calculations performed by Johnstone and Martinec for the studies by Scuderi *et al.*[3] and McKenzie *et al.*[4] raise concerns regarding the potential impact of drug packaging (unit *versus* multidose vials) and waste on the cost of drugs, including ondansetron. However, even if a minimally effective dose of ondansetron was prescribed, the costs of this drug likely would be higher than droperidol. Yet, preliminary studies would suggest that ondansetron is more efficacious than either droperidol[8] or metoclopramide* in the prevention of postoperative nausea and vomiting. As suggested in our editorial, the cost of a new drug (or therapy) should include a thorough analysis of indirect costs (*e.g.*, postanesthesia care unit stay, unanticipated hospitalization, resumption of normal activities).

Table 1. Factors Determining the Costs of Anesthetic Drugs

Direct Costs	Indirect Costs
Anesthetic drugs	Preparation and set-up time
Adjuvant agents	Excess operating room turnover time
Equipment and supplies	Recovery room stay
Drug waste	Postoperative "rescue" treatments
	Unanticipated hospitalizations
	Equipment maintenance

Johnstone and Martinec correctly pointed out the high cost of indiscriminant use of expensive drugs, such as ondansetron. Because more than 60% of patients undergoing ambulatory surgery will not experience postoperative nausea and vomiting,[9] routine prophylaxis with ondansetron cannot be recommended at this time. Yet, for selected high-risk patient populations undergoing surgical procedures associated with a high incidence of postoperative emesis, antiemetic prophylaxis may be both efficacious and cost-effective.

With the impending changes in our health-care reimbursement system, it will be important to examine our drug-usage patterns. Information on medication costs and alternative therapeutic agents is essential if we are going to practice more cost-efficiently.[10] The cost of expensive new drugs and monitoring techniques (*e.g.*, brainstem evoked potentials, esophageal echocardiography) will be scrutinized more closely in the future. Provisions for providing the cost information requested by Johnstone and Martinec should aid anesthesiologists in making informed decisions regarding the choice of drugs during the perioperative period.

Paul F. White, Ph.D., M.D., F.F.A.R.A.C.S.
Professor and Chairman
Holder of the Margaret Milam McDermott Distinguished Chair

Mehernoor F. Watcha, M.D.
Associate Professor
Director of Pediatric Anesthesia Research

Department of Anesthesiology and Pain Management
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75235-9068

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