A supplement to

CONTEMPORARY SURGERY

MARCH 2006

Integrating new agents for postoperative ileus into multimodal protocols

This program is jointly sponsored by the University of Cincinnati College of Medicine and Dowden Health Media, and is supported by an unrestricted educational grant from Adolor Corporation and GlaxoSmithKline.

Integrating new agents for postoperative ileus into multimodal protocols

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Learning Objectives

Upon completion of this activity, participants should be better able to

- Describe the pathophysiology and clinical impact of postoperative ileus (POI)
- Identify nonpharmacologic and pharmacologic approaches to preventing and/or treating POI
- Explain the rationale and clinical data that support the use of peripherally selective opioid-receptor antagonists in treatment of POI
- Discuss the incorporation of new agents that shorten the duration of POI into multimodal fast-track protocols to improve surgical outcomes

Audience

Surgeons and the advanced practice clinicians with whom they work

Sponsorship

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Program release date: March 1, 2006

Program expiration date: March 31, 2007

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- **Dr Wolff** reports that he is a consultant to or on the advisory boards of Adolor/GlaxoSmithKline and Genzyme Corporation.

The New Drug Application for alvimopan, an investigational agent, was submitted in June 2004, and is under review by the US Food and Drug Administration (FDA). Therefore, some of the information presented here will include discussion of off-label, non–FDA-approved uses. Please refer to primary references and complete product information before using or recommending any of the agents mentioned.

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This supplement to *Contemporary Surgery* was supported by an unrestricted educational grant from Adolor Corporation and GlaxoSmithKline and was developed by Continuing Edge, a division of Global Edge, Inc. It has been edited and peer-reviewed by *Contemporary Surgery*.

CONTEMPORARY SURGERY

Preface

Bruce G. Wolff, MD

Surgeons make intraoperative decisions that have profound effects on surgical outcomes. However, beyond the immediate critical needs of the operation itself, one must consider practical aspects of perioperative care, such as proper preparation and education of patients, pain management, and minimization of the risk for and/or occurrence of postoperative complications. Proper attention to these aspects of care can help lead to the best surgical outcome possible.

Postoperative ileus (POI) remains a commonly encountered clinical problem; it is often considered an unavoidable consequence of major abdominal surgery and of other types of surgery as well. The idea that POI is "unavoidable" may be changing. Consistent, effective mitigation and, possibly, even prevention of POI may soon become attainable goals of standard approaches to perioperative care. Data from controlled trials have shown that many of the methods used to date in efforts to mitigate POI—for example, use of nasogastric intubation, administration of metoclopramide, delay of solid diet—cannot be relied on to shorten the duration of POI. We have witnessed the evolution of multifaceted protocols that take into account the many potential causes of POI and that incorporate methods with clinically proven effectiveness. The search for better POI management tools has been amplified by studies demonstrating that POI has potentially significant negative clinical impact. Furthermore, many surgeons believe that their patients' experience during postoperative recovery reflects directly on their surgical skills; in short, patients' perceptions of their surgeons can be negatively impacted by POI.

The more that we learn about the potential causes of POI, the better prepared we can be to prevent it or at least minimize the risk of its occurrence. Alvimopan and methylnaltrexone comprise a new class of drugs—peripherally active mu-opioid-receptor antagonists—that targets one of the main putative etiologic factors in POI: opioid-mediated adverse activity in the gut. Advanced clinical data for alvimopan, for example, show that these agents hold promise with respect to reducing POI while preserving the beneficial analgesic effects of opioids. We may be able to reshape schemata for postoperative recovery by incorporating peripherally active mu-opioid-receptor antagonists into multifaceted protocols that include other proven methods (for example, alternate analgesia, laparoscopic surgery, early feeding) of targeting complementary aspects of POI.

The articles that follow are based in part on presentations at an independent symposium held during the American College of Surgeons Annual Meeting in San Francisco, California, on October 17, 2005.* First, the current understanding of the pathophysiology of POI, along with the latest data on its overall clinical impact, is discussed by Dr Anthony Senagore. In the second article, Dr John Leslie provides the rationale and clinical data that support the use of peripherally active mu-opioid-receptor antagonists in modern multifaceted protocols. Dr Theodore Saclarides then presents a comprehensive assessment of select methods that may be incorporated into multifaceted protocols, discussing their current relative merit and the data to support or refute their continued use. Salient points from the question-and-answer session that followed the talks also are presented for your consideration. I hope you find all of the articles to be of educational value and potentially useful to your surgical practice.

* This commercially supported satellite symposium held during the American College of Surgeons clinical congress was independent of the clinical congress educational activities and was not accredited by the American College of Surgeons.

CONTEMPORARY SURGERY

Overview of POI and its impact on surgical outcomes

Anthony J. Senagore, MD, FACS, FASCRS

Despite the plethora of reports of postoperative ileus (POI) since the early days of modern surgery, there has been no clear consensus regarding its definition, etiology, or clinical course. A variety of opinions surround POI. Some hold that POI does not, in fact, occur in all patients undergoing major surgery and that multimodal care plans already in practice can be useful when dealing with POI. Others believe that a substantial proportion of patients undergoing major surgery experience some degree of extended POI and that currently available approaches are simply ineffective in reducing POI and its clinical impact.

In the relatively recent past, we have clarified many of these uncertainties, and we have seen a renewed interest in the management, and perhaps prevention, of POI. To that end, surgeons and the advanced practice clinicians with whom they work have made a significant impact. Furthermore, they will be critical determinants in the degree of success—or failure—of emerging paradigms built on an improved understanding of the causes of POI and the multimodal strategies that have evolved as a result.

Definition and causes of POI

One helpful advance has been the trend toward an accepted definition of POI as a temporary impairment of gastrointestinal (GI) motility occurring universally after major abdominal surgery.[1,2] Notably, POI also can be associated with other abdominal and nonabdominal procedures such as hysterectomy, cystectomy, thoracic surgery, and arthroplasty.[3-5] Inasmuch as intraoperative and postoperative opioids for pain are known to frequently result in cessation of bowel motility, other causative factors are thought to be related directly to the surgical procedure itself, as first suggested by animal studies. Neurogenic (sympathetic hyperactivity), inflammatory (cellular and humoral factors, including endogenous opioid peptides), and hormonal factors all play some role in the maintenance of POI, prolonging its duration and/or leading to an increase in pain, distention, and other symptoms.[6] Support for a direct role of the surgical procedure comes primarily from observations in human studies that “bigger” operations (for example, open procedures of the colon) are more often associated with greater trauma—maximizing expression of the neurogenic, inflammatory, and hormonal factors—and, hence, the potential to induce POI of longer duration.[3,7] The impairment of muscle activity following surgery has been shown to parallel the local tissue concentration of inflammatory cells.[8] The association of less invasive surgery (for example, laparoscopy) with a lesser degree of trauma and often-reduced POI provides further support.[9] However, in some operations that take place outside the abdominal and pelvic cavity—most notably orthopedic procedures—POI is not inconsequential. Therefore, a multifactorial etiology of POI that encompasses administered opioids, “iatrogenic” factors, and other potential causes must be considered.

Symptoms of POI differ from patient to patient. Various clinical characterizations have been used but commonly include abdominal distention and/or bloating, pain, nausea and/or vomiting, inability to pass stool, and inability to tolerate a solid diet. What is becoming more clearly defined is the duration of POI in the majority of patients who experience it. Recently a controlled clinical trial helped elucidate the clinical course of untreated POI, data that had been lacking in the literature. The study, which evaluated the use of alvimopan for treatment of POI, included patients who underwent

partial small- or large-bowel resection with primary anastomosis or radical total abdominal hysterectomy. Results showed that normal GI function as defined in the study resumed after slightly more than 4 days in 50% of the subjects in the placebo group, whereas the other 50% still had POI.[10] *(For more details, see Dr Leslie's article.)* Even after 6 days, approximately 20% of patients in the placebo group still had not recovered normal GI function. Although transient, POI may be expected to last between 4 and 5 days and have a significant clinical impact in the majority of patients undergoing major abdominal surgery.[6,10]

TABLE 1

Postoperative ileus: a wide range of effects

Increased postoperative pain	Increased nausea and vomiting
Increased risk for aspiration	Prolonged time to regular diet
Delayed wound healing	Increased risk for malnutrition/catabolism
Prolonged time to mobilization	Increased pulmonary complications
Prolonged hospitalization	Increased health care costs

Risk factors for POI

Several fairly well-accepted risk factors are associated with the occurrence of POI: surgery (particularly abdominal surgery) and, to some degree, surgical technique. Regarding the latter, there is variability. Although we have accumulated considerable evidence showing a real advantage in relation to reducing the incidence of POI with, for example, laparoscopic procedures, the data are not as strong and are inconsistent for other changes in technique, such as unusual incisions.[11] To varying degrees, age, inhaled anesthesia, preexisting GI disease and/or other comorbidities, psychologic stress (in addition to the physiologic stress of surgery), and inactivity all may help increase the risk for POI.[1-3,12]

Impact of POI

Once POI occurs, its effects on a patient's recovery can be staggering. The effects range from increased pain to prolonged hospitalization and increased costs **(TABLE 1)**.[2,6,13-15] Specific costs of POI can be assigned to the use of nasogastric intubation, intravenous (IV) hydration, laboratory tests, nursing care, and increased hospital length of stay (LOS).[12,16]

The economic burden of POI is driven primarily by hospital LOS. The negative effects on the hospital include increased dissatisfaction on the part of the patient who is unable to go home and the increase in resources required to care for patients who are being hospitalized following abdominal and some nonabdominal operations.[3,4,6,17] Such patients generally require a high degree of nursing care, are typically receiving parenteral medications, and may require attention to IV medications; in short, it is expensive to care for such patients. Hospitalization of a patient with POI means one fewer bed is available for new patients who would otherwise be admitted; this can be detrimental to other patients' access to care at a high-occupancy hospital.

The costs of hospitalization alone (excluding surgical costs) are significant. One recent study reported incremental charges between $4118 and $8785 per hospitalization for POI (P<.0001).[18] In another recent analysis of resources used to care for 161,000 Medicare patients who underwent major intestinal or rectal resection between October 1999 and September 2000, it was found that such patients spent approximately 1.8 million days in the hospital at a cost of $1.75 billion.[19] Clearly, the ability to reduce the duration of POI, even by 1 day, can result in substantial reclamation of what are often severely limited hospital—and human—resources.

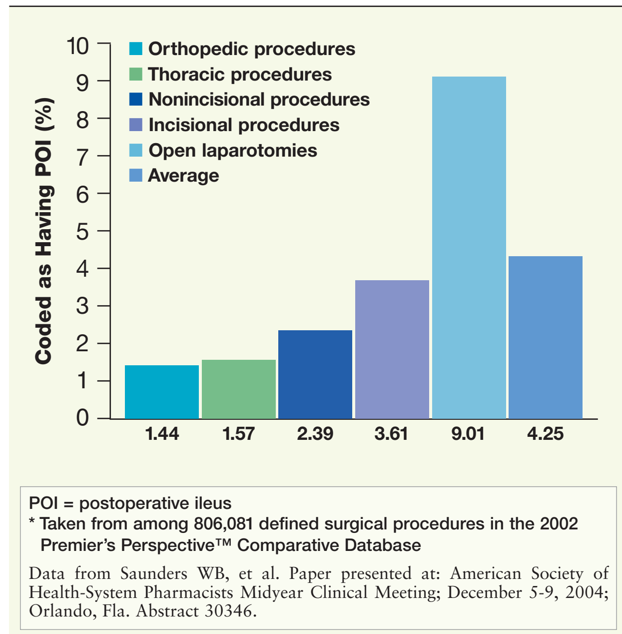
Keeping track of POI: optimizing outcomes and reimbursement

Accurate noting of the occurrence of POI—that is, coding—should be practiced routinely in order to better plan and implement multimodal strategies that reduce this postoperative morbidity. Yet prospective controlled studies that describe the incidence of POI, such as that by Wolff and colleagues,[10] are lacking. According to a large number of anecdotal reports, POI occurs after major abdominal surgery in approximately 1 of every 4 patients and lasts approximately 3 or more days. However, surveys have found that POI is coded at much lower rates.

One recent attempt to study the prevalence and economic burden of POI used 2002 data from Premier's Perspective™ Comparative Database, which includes 5 million discharges annually.[20] A total of 806,081 surgical

FIGURE 1

Percentage* of patients coded as having experienced POI after select procedures

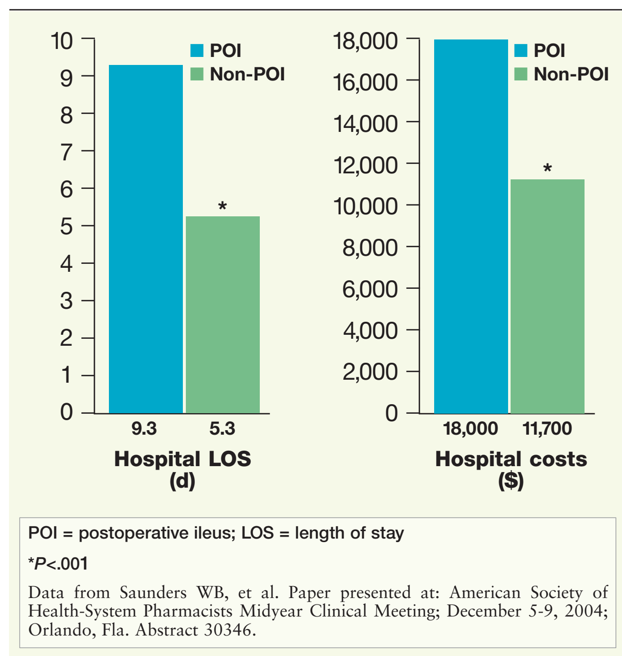


POI = postoperative ileus
* Taken from among 806,081 defined surgical procedures in the 2002 Premier's Perspective™ Comparative Database

Data from Saunders WB, et al. Paper presented at: American Society of Health-System Pharmacists Midyear Clinical Meeting; December 5-9, 2004; Orlando, Fla. Abstract 30346.

FIGURE 2

Hospitalization outcomes of patients with and without coded POI



POI = postoperative ileus; LOS = length of stay
*$P<.001$

Data from Saunders WB, et al. Paper presented at: American Society of Health-System Pharmacists Midyear Clinical Meeting; December 5-9, 2004; Orlando, Fla. Abstract 30346.

patients were identified for evaluation of the rate of POI after orthopedic and thoracic surgeries, nonincisional and incisional procedures, open laparotomies, and other procedures based on 645 primary surgery codes. Postoperative ileus was identified using ICD-9 diagnosis codes 560.1 (paralytic ileus) and 997.4 (digestive system complications). As may be expected, open laparotomy was associated with the greatest incidence of coded POI: 9.01% **(FIGURE 1)**. Unexpectedly, this incidence was only about 6 to 7 times greater than that for POI coded in orthopedic procedures and only about a third to a half of the rate of commonly observed POI. After comparison with published estimates of the incidence of POI, the authors concluded that "in practice, POI may not be routinely coded and therefore, the overall recorded rate and economic burden of illness found in our study may be underestimated."[20] For coded POI, hospital LOS was significantly longer (9.3 vs 5.3 days, $P<.001$) and associated cost significantly higher ($18,000 vs $11,700, $P<.001$) **(FIGURE 2)**.

A similar, more detailed analysis also evaluated 2002 data from Premier's Perspective™ Comparative Database but only for POI following open laparotomy.[21] Included patients had a hospital LOS shorter than 30 days, an operation that lasted less than 12 hours, and a minimal hospital cost of $500. Postoperative ileus was identified using ICD-9 diagnosis codes 560.1 and 997.4. Among the 117,417 cases of coded POI identified, LOS was 10.6 days, compared with 5.4 days for patients in whom POI was not coded ($P<.05$) **(TABLE 2)**. Mean total costs were $16,303, compared with $9944 for those with coded or uncoded POI, respectively ($P<.05$).

Reimbursement may be an incentive to accurately and consistently code POI whenever it occurs. Notably, the word ileus must appear in the record to be valid for proper coding. Other clinical characterizations may be used simultaneously, but only "ileus" will result in proper coding and reimbursement for POI. To bring that issue into sharp focus, a DRG code of 148—major small-bowel and large-bowel procedures with complications—is eligible for $20,000 in reimbursement (under Medicare), compared with $8000 for a DRG code of 149 (major small-bowel and large-bowel procedures without complications). The DRG-148 reimbursement is just slightly higher than the average costs for extended LOS due to POI in the analyses by Saunders[20] and Senagore[21] (greater than $18,000 and $16,000, respectively). When patients with POI are incorrectly recoded as a DRG-149, hospital and/or practice revenue issues

TABLE 2

Coding of POI after open laparotomy: risk factors and economic burden

	No Coded POI	Coded POI
N	175,992	117,417
Mean age (y)	50.8	59.8*
Mean OR time (h)	2.5	3.0*
Mean LOS (d)	5.4	10.6*
Opioid PCA (%)	31.3	41.8*
Opioid epidural (%)	2.8	3.7*
Severe or most severe illness (%)	20.7	48.4*
In-hospital mortality (%)	2.3	3.7*
Mean total costs	$9944	$16,303*

POI = postoperative ileus; OR = operating room; LOS = length of stay; PCA = patient-controlled analgesia.
*P<.05

Data from Senagore A, et al. In: Program and abstracts of the 2005 annual meeting of the American Society of Colon and Rectal Surgeons; April 30-May 5, 2005; Philadelphia, Pa. Podium presentation, S22, p. 165.

become cause for concern because such patients will have a much longer LOS, and the actual costs of caring for them may be disproportionately higher than the reimbursed amount.

Conclusion

In many institutions, primary responsibility for continuity of care and oversight of the management of postoperative recovery falls to the surgeon. Surgeons and the advanced practice clinicians with whom they work can help patients avoid some of the preventable components of POI by engaging patients in their recovery and informing them of postoperative benchmarks. Encouraging patients to eat solid food when they can tolerate it may help reduce the risk for ileus. (Note: Hospital policy often determines whether patients should be kept in the hospital until they can tolerate solid foods.) Perioperative hydration is another potentially useful tool, but this and other supportive approaches by themselves will not prevent POI in every case. *(See Dr Saclarides' article for more details.)* Pain management remains a critical concern with respect to the development of POI, and decreasing the exogenous opioid burden probably can help reduce the incidence of POI. If opioid-mediated analgesia can be preserved in a setting of reduced POI (as data with new opioid-receptor antagonists suggest), this may be especially helpful for achieving maximum patient satisfaction. *(See Dr Leslie's article.)* A new paradigm that involves multimodal rehabilitation programs for improvement of overall postoperative morbidity, including POI, likely will include evolving techniques and novel pharmacologic agents.[22] Implementing new multimodal strategies for the management and potential prevention of POI will help surgical teams attain optimal compliance with both preoperative and postoperative care plans.

The author wishes to acknowledge the editorial contributions of Michael Pellegrino, PhD, and the technical assistance of Robert Coover.

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Rationale for integrating new GI-selective agents into multimodal protocols

John B. Leslie, MD, MBA

It is fairly clear that the surgical component of the etiology of postoperative ileus (POI) may be related to the trauma and manipulation of the bowel and to the release of endogenous endorphins, catecholamines, enkephalins, dynorphins, and other endogenous factors. The stimulation of somatic and visceral fibers also may play a role.[1-3] Even in cases where no violation of the intraperitoneal cavity has occurred, some patients will develop significant POI, which causes them extreme discomfort and lengthens their hospital stay. How can we explain the occurrence of POI following orthopedic and cardiac surgeries?

The causes of POI are multifactorial; however, a common pathway may involve the action of some of the aforementioned endogenous factors, as well as the consequences of the routinely used anesthetic and postoperative pain management approaches. This common pathway is mediated in part by the activity of stimulated mu-opioid receptors located throughout the gastrointestinal (GI) tract and central nervous system (CNS).[4-6]

The severity and duration of POI may be determined largely by how we care for patients in our normal perioperative routine. Moreover, the new GI-selective agents may be integrated into multimodal protocols. Thus it may now be possible for us to approach POI from a perspective of prevention rather than treatment.

The dilemma posed by opioid use

Because pain is now considered to be the fifth vital sign, many institutions have undertaken extraordinary measures to ensure that patients receive adequate and satisfactory analgesia.[7,8] Such measures often involve the use of intraoperative and postoperative opioids, patient-controlled analgesia (PCA) regimens, and other anesthetic and/or analgesic agents that together may contribute substantially to the postoperative problems experienced by many patients. The problems caused by opioids include not only POI but also other GI effects, such as nausea and vomiting, and CNS effects, such as sedation, hypotension, respiratory depression, sweating, urinary retention, and pruritus.[9] Generally patients consider bowel dysfunction to be the most common, and often most debilitating, effect.[10,11] The benefit of opioid analgesia in both acute nonmalignant (ie, postoperative) pain and cancer pain is often limited by the development of symptoms related to the adverse effects of opioids on gut motility.[11,12] However, use of opioid-sparing regimens (for example, nonsteroidal anti-inflammatory drugs) or limitation of postoperative opioid use (that is, decreasing the duration and/or amount of opioid exposure) may compromise effective pain management.

The specific pharmacologic actions of opioids in the GI tract cause numerous adverse clinical consequences, including increased GI reflux, straining, incomplete evacuation, bloating, abdominal distention, spasm, abdominal cramps and pain, biliary colic, epigastric discomfort, impaired ability to evacuate the bowel, and hard, dry stool.[9,12] These effects are mediated primarily through opioid binding to mu-opioid receptors located in the gut, the same type of opioid receptor that mediates opioid analgesia in the CNS.[4-6] In reviewing these consequences, it is no wonder that patients might prefer to tolerate debilitating pain, rather than undergo pain-management regimens that interfere with GI function.[13]

Opioid analgesics are widely used for postoperative pain management, yet they all disrupt coordinated GI motility.[4,9] The duration of POI is proportional to exposure and dose of opioid analgesia. One representative study of 40 colectomy recipients found a correlation

between morphine PCA dose and time to first bowel sounds (P = .001), flatus (P = .003), and first bowel movement (P = .002).[14] Conversely, early studies of restricted opioid use and alternative analgesics for pain showed a reduction in duration of POI.[15-18] Clearly, the ability to retain the benefits of opioid-mediated analgesia while minimizing the adverse GI effects of postoperative opioids would be a major advance in surgical practice. A new class of opioid-receptor antagonists that are active specifically at gut mu-opioid receptors may represent such an advance.

Older tertiary opioid-receptor antagonists

Opioid-receptor antagonists have been developed in the past but with little or no success in separating the unwanted effects of opioids in the gut from the desirable effects on the CNS. Increased understanding of opioid receptor physiology has led to novel strategies to limit the systemic absorption of mu-opioid-receptor antagonists and prevent their absorption through the blood-brain barrier (BBB), and, thus, penetration of the CNS.

Opioid-receptor antagonists that have been available to date—such as naloxone and nalmefene, the so-called tertiary opioid-receptor antagonists—have been used in attempts to mitigate POI. Unfortunately, at doses that may block the effects of opioids in the gut, these tertiary antagonists also block opioids' CNS effects, reversing analgesia or causing symptoms of opioid withdrawal. Naloxone readily crosses the BBB; it can cause symptoms of systemic withdrawal.[9,19] A recent study confirmed that even at low doses, naloxone also reverses analgesia.[20] As naloxone's opioid-antagonistic activity can be useful in nonsurgical settings, some clinicians still assume that naloxone also may help reduce the adverse GI effects of perioperative opioid administration. However, naloxone is not indicated for treatment of POI.

Newer peripherally acting mu-opioid-receptor antagonists

Refinements in the structure of tertiary opioid-receptor antagonists have led to the development of quaternary opioid-receptor antagonists. (The chemistry of opioid-receptor antagonists has been discussed elsewhere.[21]) Because of structural changes, these new drugs cannot pass the BBB and do not interact with centrally located receptors; thus, they are peripherally acting. There now exist 2 such agents in advanced clinical development: methylnaltrexone (MNTX), created by the addition of a methyl group to the tertiary opioid-receptor antagonist naltrexone (itself based on the opioid-receptor agonist morphine),[22] and alvimopan, a new quaternary mu-opioid-receptor antagonist structurally similar to the opioid-receptor agonist fentanyl but engineered to bind to mu-opioid receptors in the GI tract and not to central mu-opioid receptors.[5,21,23]

The clinical application of opioid-receptor antagonists likely will differ depending on the clinical scenario, that is, whether they are used for constipation resulting from the chronic administration of opioids (as in cancer cases) or for ileus resulting from the acute, postoperative use of opioids. Although further explanation of the clinical pharmacology of the new agents is beyond the scope of this article, briefly, the difference in use may reflect differences in clinical pharmacology involving sensitization of gut mu-opioid receptors following chronic opioid use. However, because of the dosing implications, it is important to keep that difference in pharmacology in mind when comparing clinical trials of peripherally acting mu-opioid-receptor antagonists. For example, trials evaluating alvimopan for POI have evaluated twice-daily 6-mg and 12-mg dosages over a 7-day period (see details below); trials studying alvimopan for chronic constipation in patients receiving chronic opioid therapy have evaluated lower dosages—once-daily 0.5-mg or 1-mg dosages over 21 days—and will not be discussed here.[24]

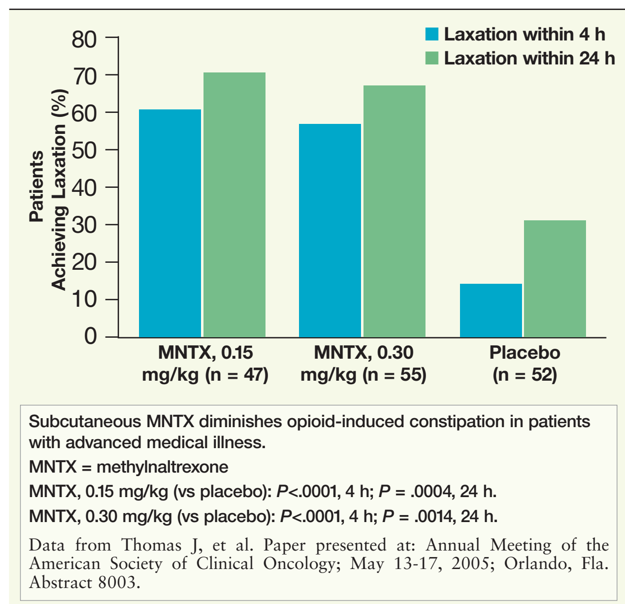
Methylnaltrexone

To date, MNTX has been evaluated in more than 650 healthy volunteers and patients in various clinical trials. These include 2 phase 3 trials—one completed and one ongoing but with target enrollment attained—for opioid-induced constipation in patients with advanced medical illness (including cancer, AIDS, and heart disease) and a phase 2 trial in patients at risk for bowel dysfunction following segmental colectomy. Phase 2 studies in patients with chronic pain are planned, as are phase 3 studies to evaluate MNTX for the amelioration of the acute, postoperative adverse effects of opioids.[25] *(See Dr Saclarides' article for more details.)*

Although not informative regarding any potential use of MNTX for POI, results from a phase 3 trial in

FIGURE 1

Results from study MNTX 301



Subcutaneous MNTX diminishes opioid-induced constipation in patients with advanced medical illness.
MNTX = methylnaltrexone
MNTX, 0.15 mg/kg (vs placebo): *P*<.0001, 4 h; *P* = .0004, 24 h.
MNTX, 0.30 mg/kg (vs placebo): *P*<.0001, 4 h; *P* = .0014, 24 h.
Data from Thomas J, et al. Paper presented at: Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, Fla. Abstract 8003.

chronic opioid-using patients have helped demonstrate the ability of MNTX to reverse some of the adverse GI effects of opioids (in this case, constipation). MNTX301 was a double-blind, randomized, placebo-controlled study that enrolled 154 patients with advanced medical illness and opioid-induced constipation; they had no laxation (bowel movement) for 48 hours despite the use of laxatives and stool softeners.[26] Methylnaltrexone, 0.15 mg/kg or 0.30 mg/kg, was given subcutaneously. The primary endpoint, laxation within 4 hours, was achieved in 62% and 58% of patients treated with MNTX, 0.15 or 0.30 mg/kg, respectively, compared with 13% of patients treated with placebo (*P*<.0001) **(FIGURE 1)**. The median time to laxation was 70 minutes for patients in the 0.15 mg/kg arm; 45 minutes for those in the 0.30 mg/kg arm; and more than 24 hours for patients treated with placebo (*P*<.0001). Preliminary safety data showed that MNTX was generally well tolerated. The most frequently reported adverse events were flatulence and transient abdominal cramping, the latter of which occurred in more than 30% of patients in the 0.15 mg/kg arm and in more than 40% of patients in the 0.30 mg/kg arm.

Data regarding preservation of analgesia in the presence of MNTX were not provided. The authors reported no increased systemic opioid withdrawal due to study medication, but local opioid withdrawal may have led to the adverse GI effects (for example, cramping) observed in that study. Chronic opioid therapy may lead to sensitization of gut mu-opioid receptors; administration of an opioid antagonist, such as MNTX, in the presence of sensitized gut opioid receptors may cause GI symptoms of opioid withdrawal such as abdominal cramping.[23]

Alvimopan

An early proof-of-principle trial involving 78 surgical patients showed that alvimopan improves postoperative recovery of bowel function and shortens hospital stay without compromising opioid-mediated analgesia.[27] Since then, alvimopan has been evaluated specifically for its usefulness in mitigating POI and associated clinical effects in more than 2100 patients in 3 US-based phase 3 clinical trials; another phase 3 trial of 660 patients with POI is ongoing. The development and clinical experience with alvimopan to date (with the exception of the ongoing phase 3 trial) is the subject of recent reviews.[23,28-30] In all phase 3 studies of this new agent, investigators have assessed GI function, pain and the preservation of analgesia, and the drug's ability to accelerate hospital discharge.

Studies 14CL313 and 14CL302 were both randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials of alvimopan for the management of POI across 34 North American centers and 40 US centers, respectively.[31,32] In study 313, Wolff and colleagues compared oral alvimopan, 6 mg or 12 mg, with identical placebo capsules, given at least 2 hours before surgery and then twice daily beginning on postoperative day (POD) 1 until hospital discharge, up to a maximum of 7 PODs. The study included 510 patients scheduled to undergo a partial small-bowel or large-bowel resection with primary anastomosis or radical total abdominal hysterectomy.[31] In study 302, Delaney and colleagues evaluated the efficacy and safety of oral alvimopan in 451 patients undergoing major abdominal surgery (specifically, segmental colon resection or simple/radical hysterectomy).[32] Dosing of alvimopan in study 302 was similar to that in study 313: patients were stratified by surgery type and randomized in a 1:1:1 ratio to receive alvimopan, 6 mg; alvimopan, 12 mg; or placebo, with a sip of water at least 2 hours before surgery and then twice daily beginning on POD 1 until hospital discharge, for a maximum of 7 days.

In both phase 3 studies, the approaches to postoperative pain management were engineered to offer the best recovery experience and outcomes.[31,32] Eligible patients in study 302 were scheduled to receive postoperative intravenous (IV) PCA with opioids, and intraoperative naso-

gastric (NG) tubes were to be removed at the end of surgery or by the morning of POD 1. In study 313, eligible patients were scheduled to receive postoperative IV PCA with opioids and to have their NG tubes removed at the end of surgery. Furthermore, liquids were offered and ambulation encouraged on POD 1, and solid food (to encourage early feeding) was offered on POD 2. Therefore, any beneficial effect of alvimopan observed in those patients receiving the study drug would be over and above the beneficial effects afforded by the multimodal fast-track strategies used for all patients.

Alvimopan had an excellent safety profile and was tolerated well in both studies.[31,32] In study 313, the primary endpoint of GI-3—which assessed return of normal GI function by time to toleration of first solid food and to bowel movement (BM) or flatus, whichever occurred last—was significantly achieved with both doses of alvimopan **(TABLE)**.[31] In study 302 alvimopan, 6 mg twice daily, significantly reduced time to solid food and a BM or flatus; time to solid food and a BM; time to writing of discharge order; and time to discharge based solely on recovery of GI function **(TABLE** and **FIGURE 2)**.[32] The apparent lack of a statistically significant dose response in study 302 for those in the 12-mg group—in contrast to the high level of statistical significance of data obtained in study 313—may have been due to the higher discontinuation rate in that arm and the resulting disproportionate representation of the different patient subpopulations; a positive trend in the 12-mg group was noted, however.

TABLE

Select efficacy results from 2 phase 3 trials of alvimopan for POI following major abdominal surgery*

ENDPOINT/TREATMENT	STUDY 302			STUDY 313		
	n	Mean, h (▲vs Placebo)†	*P* Value	n	Mean, h (▲vs Placebo)†	*P* Value
Time to first solid food + BM or flatus (GI-3)						
• Placebo	145	100.3	—	149	120	—
• Alvimopan, 6 mg	141	86.2 (-14.1)	.003	155	105 (-15)	<.05
• Alvimopan, 12 mg	138	92.8 (-7.5)	.059	165	98 (-22)	<.001
Time to first solid food + BM (GI-2)						
• Placebo	145	115	—	149	133	—
• Alvimopan, 6 mg	141	100 (-15.2)	.007	155	113 (-20)	.013
• Alvimopan, 12 mg	138	104 (-10.5)	.057	165	105 (-28)	<.001
Time to writing of hospital discharge order						
• Placebo	145	122	—	149	146	—
• Alvimopan, 6 mg	141	108 (-14)	<.001	155	133 (-13)	.070
• Alvimopan, 12 mg	138	115 (-7.2)	.17	165	126 (-20)	.003

Oral alvimopan, 6 mg or 12 mg, or placebo capsules, were given at least 2 hours before surgery and then twice daily beginning on postoperative day 1 until hospital discharge, for a maximum of 7 postoperative days.

POI = postoperative ileus; BM = bowel movement

*451 patients undergoing segmental colon resection or simple or radical hysterectomy (study 302) and 510 patients scheduled to undergo a partial small- or large-bowel resection with primary anastomosis or radical total abdominal hysterectomy (study 313).

†Means estimated using area under the Kaplan-Meier cumulative curve.

Data from Delaney CP, et al. *Dis Colon Rectum.* 2005;48:1114-1125; Wolff BG, et al. *Ann Surg.* 2004;240:728-734.

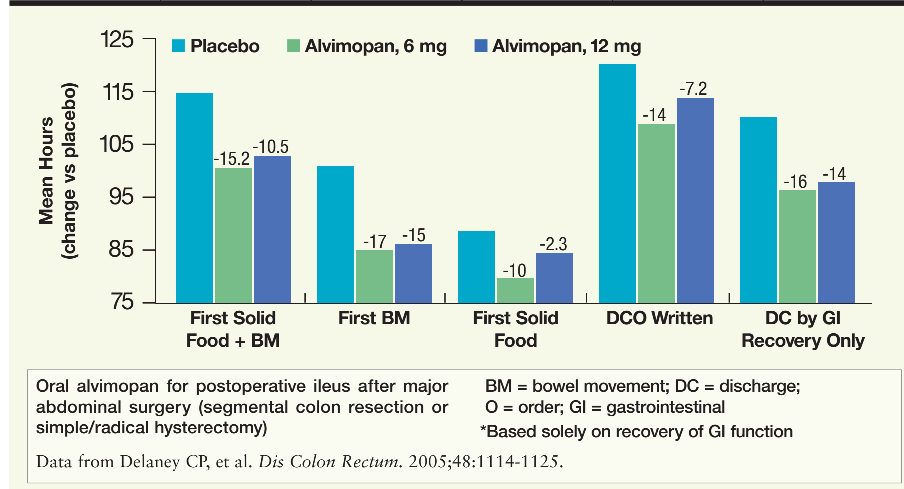
Phase 3 study results to date show that alvimopan effectively reduces the duration of POI by 1 day. The time to writing of hospital discharge orders is shorter for those receiving alvimopan; it is reasonable to infer that the decrease in time is a direct result of the reduction in POI and the acceleration in recovery of GI function. An ongoing phase 3 trial (Study 14CL314) of alvimopan in patients who have undergone bowel resection should help define the use of this drug further. In this study, 660 patients are randomized to placebo or 12 mg of alvimopan twice daily with the initial dose administered 30 to 90 minutes prior to surgery. This is in contrast to 2 alvimopan dosing groups and the 2-hour minimum window for the first alvimopan dose used in other phase 3 trials. Also of clinical relevance, the primary endpoint in the study will be GI-2, rather than GI-3. This stricter composite measure of recovery of both upper-GI and lower-GI function, defined by time to toleration of solid foods and time to first BM, whichever occurs last, eliminates the subjective determination of "first flatus." Initial results from study 314 may become available as early as mid-2006.

Two other important clinical considerations are maintenance of adequate analgesia while using opioid-receptor antagonists and hospital readmission rates with fast-track multimodal protocols. Readmission may be an especially important indicator of the reliability

FIGURE 2

Results from study 302

P Values	Time to First Solid Food + BM	Time to First BM	Time to First Solid Food	Time to Writing DCO	Time to DC*
Alvimopan, 6 mg	.007	.002	.033	<.001	<.001
Alvimopan, 12 mg	.057	.006	.37	.17	.004



Oral alvimopan for postoperative ileus after major abdominal surgery (segmental colon resection or simple/radical hysterectomy)

BM = bowel movement; DC = discharge; O = order; GI = gastrointestinal

*Based solely on recovery of GI function

Data from Delaney CP, et al. *Dis Colon Rectum*. 2005;48:1114-1125.

of fast-track protocols (that is, the potential increase in risk for readmission due to postoperative complications in exchange for faster discharge). Fast-track protocols including alvimopan do not increase readmission, and they may reduce readmission rates. In study 313, the numbers of alvimopan recipients who were rehospitalized for any reason within 10 days of discharge were half those in the placebo group: approximately 4% and 8%, respectively.[31] Pain scores were similar among all groups in studies 302 and 313, indicating that alvimopan did not reverse opioid-mediated analgesia; that is, it specifically acted only on gut mu-opioid receptors.[31,32] Furthermore, in both phase 3 studies, a dose-dependent trend of reduced nausea and vomiting was observed among alvimopan recipients. This may be a result of alvimopan's inhibition of gut mu-opioid receptor mediated activity.

Multimodal programs and new opioid-receptor antagonists

Mounting evidence suggests a potentially critical role for the new GI-selective opioid-receptor antagonists with respect to POI. A recent study of GI transit used upper-GI and lower-GI radiolabeled markers of bowel transit time to evaluate alvimopan in 74 healthy volunteers.[33] Patients were given alvimopan, 12 mg; codeine, 30 mg; codeine, 30 mg, plus alvimopan, 12 mg; or placebo **(FIGURE 3)**. Gut function and motility were based on movement of the markers over time. Patients who received codeine had a significant increase in colonic transit time. Alvimopan alone resulted in a decrease in colonic transit time, with the marker traveling much farther. When alvimopan was administered with codeine, gut motility as measured by translocation of marker resembled that of normal bowel function. After 48 hours, the majority of patients who received alvimopan had emptied their colon (geometric center [GC] value between 4.5 and 5), while the markers in those patients who had received only codeine transited approximately halfway down their colon (GC value between 2 and 2.5). Notably, results for patients who had received the combination of codeine plus alvimopan were nearly exactly the same as those for patients in the placebo group.

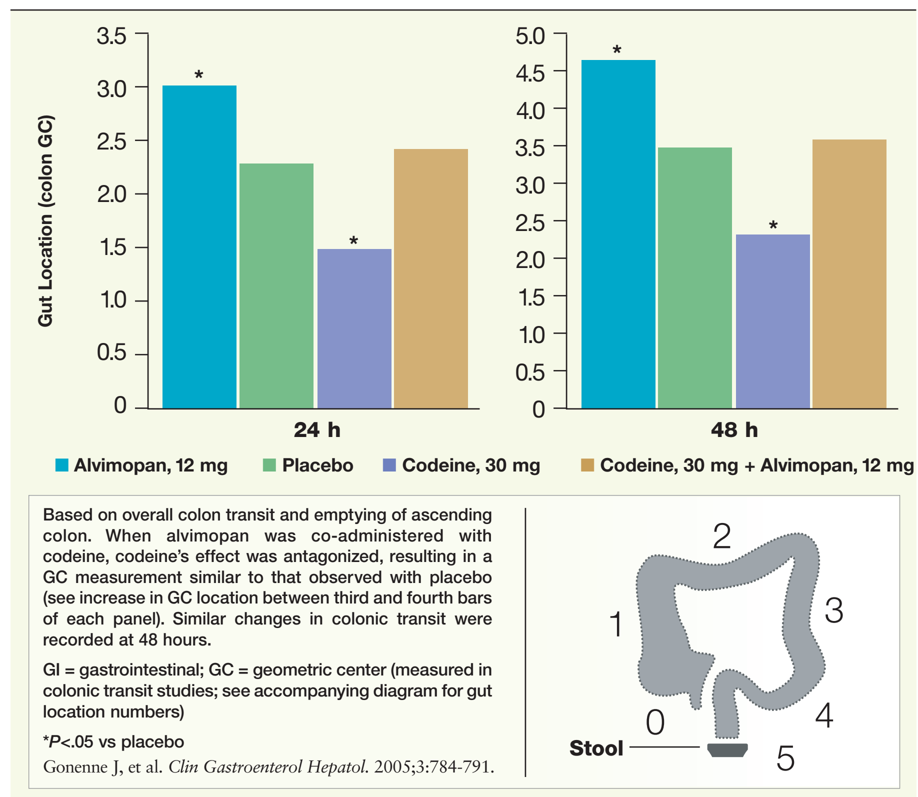
Conclusion

Today, pain is considered an almost unnecessary consequence of surgery, thanks to effective PCA and other analgesia regimens. Yet opioid-mediated analgesia has significant adverse effects that can be costly. Recent trials suggest that the new peripherally acting mu-opioid-receptor antagonists shorten the duration of POI in patients who have undergone major abdominal surgery without compromising pain management. More data from controlled clinical trials are needed in order to define the role of these GI-selective agents in postoperative multimodal care programs. Rescue or treatment trials in patients with uncomplicated POI also must be conducted. Preservation of opioid-mediated analgesia, acceleration of time to hospital discharge and time to normal feeding, and reductions in postoperative nausea

all may be realistic expectations for emerging multimodal protocols that include methods of reducing the burden of opioids' adverse GI effects.

The author wishes to acknowledge the editorial contributions of Michael Pellegrino, PhD, and the technical assistance of Robert Coover.

FIGURE 3



Based on overall colon transit and emptying of ascending colon. When alvimopan was co-administered with codeine, codeine's effect was antagonized, resulting in a GC measurement similar to that observed with placebo (see increase in GC location between third and fourth bars of each panel). Similar changes in colonic transit were recorded at 48 hours.

GI = gastrointestinal; GC = geometric center (measured in colonic transit studies; see accompanying diagram for gut location numbers)

*P<.05 vs placebo

Gonenne J, et al. *Clin Gastroenterol Hepatol.* 2005;3:784-791.

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CONTEMPORARY SURGERY

Multimodal options for POI: what works?

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The notion of preplanned, innovative protocols to enhance postoperative recovery and clinical outcomes has been gaining greater acceptance in both the United States and abroad, with well-designed strategies appearing in recent literature.[1-4] Postoperative ileus (POI) may represent an ideal opportunity to establish standardized interdisciplinary protocols that reduce postoperative morbidity. Various approaches have appeared over the years in attempts to reduce POI and involve all surgical-team members to a greater or lesser degree.

Subsequent to the surgeon's choice of an appropriate operation for the patient, the entire surgical team becomes involved in the operation. Typically the team includes a nurse who admits patients and begins administering subcutaneous heparin for prophylaxis against deep vein thrombosis (DVT), as well as an anesthesiologist who plans proper pain management. A fast-track protocol also may involve a peri-anesthesia nurse who administers agents to assist in anesthesia or employs methods to improve postoperative morbidity (for example, to reduce risk for POI) and a recovery-room nurse who implements preprinted orders that have established a fast-track protocol. In addition, surgical residents play a role, making rounds at the appropriate time of day to write discharge orders as needed.

Management approaches for POI: current debates

Laxatives, prokinetic drugs, opioid-sparing regimens (including use of nonsteroidal anti-inflammatory drugs), early feeding, use of epidural local anesthetics, and less-invasive laparoscopic surgical techniques are all associated with varying degrees of success in improving POI. However, which of these measures are better suited for inclusion in fast-track multimodal protocols?

Fast-track strategies should include only methods or pharmacologic agents that have been documented as effective in helping to reduce the duration of POI or diminish the risk of its development. Adopting such criteria for deciding which approaches might offer a better chance of improvement in POI represents a subtle yet important shift in the way surgeons are beginning to think about this condition. Rather than depending on anecdotal or limited clinical evidence for the methods used to manage POI once it occurs, sufficient data have accumulated to a point at which surgeons and their teams can begin to think about reducing the risk for POI or even preventing its occurrence through proven effective and novel approaches. Certainly the "classic" view of POI as an inevitable response to major surgery that prolongs hospitalization and significantly diminishes patients' quality of life still holds true.[5,6] However, emerging data suggest that proactive, rather than reactive, treatment of POI can decrease length of stay (LOS), facilitate hospital discharge, and improve overall outcomes.[7-9] Reassessment and possibly abandonment of much of the older dogma regarding POI and its management must go hand-in-hand with new strategies and agents for treatment of POI.

Impact of POI on LOS

Any new or alternate paradigm for POI must incorporate the steadily growing interest in hospital LOS. Evidence for an increased interest in LOS-related issues can be found in relevant literature that has appeared over the past 2 decades. For example, a literature search using the key words "length of stay" retrieved 13 publi-

cations that appeared between 1985 and 1990. None of those papers reported on clinical trials that specifically examined LOS and none discussed methods of shortening LOS. However, a subsequent literature search revealed that during the 1995-2000 time period, 122 publications included randomized, prospective, cohort comparison trials that were related to LOS.

Certainly POI can increase LOS, but LOS also is determined by a number of other factors such as pain, nausea, vomiting, fatigue, mechanical factors (drain care, instruction regarding stoma care), and delayed organ function. Fast-track multimodal programs that use defined treatment strategies and a team approach to streamline processes from admission through discharge may positively affect any or all of these factors. Yet POI by itself has been shown to contribute greatly to increased LOS *(see Dr Senagore's article)*; therefore, a reduction in the duration of POI could have a profound effect on the clinical, economic, and human costs associated with prolonged hospitalization.

TABLE 1 lists some of the more familiar methods that have been employed in attempts to reduce POI. Following is a summary of select old and new approaches to managing POI, evidence for their effectiveness—or lack of effectiveness—in POI, and some suggestions as to what might be included in new multimodal strategies of managing POI.

TABLE 1

Approaches to management of postoperative ileus

Supportive care	• Nasogastric tube avoidance • Fluid restriction • Early oral/enteral feeding
Pain management	• Epidural analgesia as part of multimodal therapy
Pharmacologic options	• Traditional medications • Opioid-sparing approaches • New-generation mu-opioid-receptor antagonists
Surgical options	• Laparoscopy vs open surgery

Challenging surgical traditions

Despite long-standing acceptance of various approaches to managing POI, some approaches are not supported by high-quality data. Examples include the routine use of nasogastric (NG) tubes following surgery, delay of feeding until flatus or bowel movement occurs, and advancement of diet in a stepwise fashion to avoid complications. Similarly, data showing improvements in POI using "standard" pharmacologic approaches (for example, metoclopramide) are lacking. More details regarding use of NG tubes and metoclopramide, as well as other agents, appear below.

Nasogastric intubation

For every patient who may need NG intubation, there are 20 who do not. Nasogastric intubation had been routine for decades, in the belief that gastric decompression aided the resolution of POI. However, extensive reviews of trials and clinical experience have found that NG intubation does not improve POI and, indeed, may exacerbate it.[10] Removal of NG tubes after anesthesia is recommended to avoid other adverse effects, which can include pneumonia, as well as fever, atelectasis, and an increase in the number of days to toleration of solid diet.[7]

Metoclopramide

Despite widespread belief that metoclopramide reduces POI, there are no data from randomized controlled trials to support this notion.[11] Metoclopramide is indicated not for POI but rather for symptomatic gastroesophageal reflux and diabetic gastroparesis (diabetic gastric stasis).[12] The majority of trials that have evaluated metoclopramide suggest no benefit for POI.[7,11,13] For example, metoclopramide given intravenously (IV) on the day of surgery at doses ranging from 10 mg every 6 hours to 20 mg every 8 hours has shown no benefit for POI in any outcome(s), and notably, metoclopramide-related adverse events occur in 15% to 20% of patients. The long-term side effects of metoclopramide, especially in elderly patients and certain other patient populations, are of greater concern. A recent review found that central-nervous-system side effects—in particular, tardive dyskinesia—accumulate with long-term use of metoclopramide.[14]

Other agents

Erythromycin and neostigmine occasionally are used in attempts to mitigate POI, but neither has any real positive effect, despite mechanisms of action that might suggest otherwise and the fact that POI is largely related to colon dysfunction (rather than disrupted gastric or

small-intestine motility).[7,11] Cisapride does in fact improve POI; however, this drug is no longer available in the United States because it increases the risk for serious adverse cardiac effects.

The absolute benefit of laxatives with respect to helping reduce POI remains unproven; studies have shown variable results.[11] Laxatives do not address the opioid-mediated etiology of POI or postoperative bowel dysfunction.[15] A study of aggressive postoperative bowel stimulation with magnesium hydroxide showed an early return (3 days) of bowel function following radical hysterectomy.[16] However, only 20 patients were evaluated and no control group was included.

Potential components of multimodal protocols for POI

Reliable data have been accumulating for some other methods (listed in **TABLE 1**) of improving POI and/or its clinical impact, such as early feeding, epidural analgesia, laparoscopic surgery, and novel opioid-receptor antagonists. Multimodal protocols that consist of management strategies and/or drugs with proven effectiveness have been shown to significantly reduce POI, decrease time to hospital discharge, and improve overall outcomes.

Early feeding

The use of this approach has been tempered by fears of complications such as increased risk for anastomotic leakage. More recent clinical data demonstrate that early feeding may reduce POI and hospital LOS following gastrectomy, colonic surgery, and gynecologic surgery.[17-19] An analysis of studies that compared early postoperative feeding with traditional feeding to reduce the duration of POI revealed a statistically significant benefit with early feeding.[7] Early feeding, which usually involves offering patients a clear liquid diet as soon as the first day of surgery, is a measure intended, in part, to help ameliorate the stress response to surgery. Although not consistently proven in controlled trials, clinical benefits may consist of improved muscle strength, accelerated healing, decreased infection rates, and earlier flatus and bowel movement. An early meta-analysis found that early enteral feeding reduced postoperative septic complications.[20] Anecdotal evidence suggests that early postoperative feeding may be tolerated in as many as 80% to 90% of patients, despite the absence of bowel sounds, flatus, or stool. Randomized prospective clinical trials of fast-track protocols that include early feeding suggest that these percentages may be accurate (see discussion of CREAD opposite). Nevertheless, prior to implementation of early feeding for all postoperative patients, assessments should be performed so that early feeding can be carefully tailored to individual patients' needs.

Epidural anesthesia

Epidurals also attenuate the stress response, are associated with fewer pulmonary complications, facilitate mobility, and improve pain control, primarily by blocking afferent input from the wound site. However, they do not reduce the risk for leakage, decrease blood loss or the need for transfusions, or lower the risk for DVT. Two major problems with epidurals are that, when offered the choice, 15% to 20% of patients refuse their use, and that even when epidural catheters are inserted, approximately one third of them dislodge, become blocked, or leak. The need for expert placement of epidural catheters further complicates these considerations. For surgeons, a main consideration is whether to use IV PCA or epidural anesthesia. However, when making this decision, one must also consider patients' happiness and satisfaction, as well as their perception that every effort is being made to manage their pain.

There is lingering debate regarding the extent to which this method benefits most patients, not only for pain management but also for reduction of POI. Most reviewed studies show that epidural anesthesia does in fact help reduce the incidence of POI.[7] A recent Cochrane review concluded that epidural local anesthetic reduced the time to recovery from POI by 36 hours when compared with systemic opioids and that it reduced the duration of POI by 24 hours compared with epidural opioids.[21] However, more studies are needed that examine the effects of epidural anesthesia with and without opioids for pain and gastrointestinal (GI) function; many studies to date have evaluated one or the other method alone.

Minimally invasive surgery and multimodal perioperative care

The potential advantages of less invasive surgical techniques, especially laparoscopy, include diminished pain, faster recovery (and return to work), better cosmesis, fewer long-term complications (adhesions, hernia), faster return of GI function, and shorter LOS.

A study comparing laparoscopic-assisted colectomy (LAC) with open colectomy in patients who had nonmetastatic colon cancer found that LAC was associated

with overall improvement in morbidity and postoperative complications, including decreases in time to oral intake (P = .001), need for NG intubation (P = .08), LOS, and persistence of POI.[22] The mean LOS was lower for the LAC group than for the open-colectomy group (5.2 vs 7.9 days, P = .005), and mean duration of persistent POI was 3 vs 9 days, respectively, for those same groups (P value not provided). Time to initiation of peristalsis was also significantly shorter in the LAC group (36 hours vs 55 hours, P = .001).[22]

The recent Colon Cancer Laparoscopic or Open Resection (also known as COLOR) Trial included 627 patients with cancer who underwent laparoscopic surgery and 621 patients with cancer who underwent open colectomy. Patients in the open-colectomy group exhibited overall improvement in perioperative characteristics and, notably, earlier recovery of bowel function (P<.0001) and shorter LOS (P<.0001).[23] A significantly shorter LOS also was reported in a comparison of LAC with open colectomy in patients with colon cancer (5 days vs 6 days, respectively, P<.001).[24]

Over the past several years, similar clinical improvements have been reported for other patient populations who have undergone abdominal surgery. One relatively early study of patients undergoing resection for ileocolic Crohn's disease demonstrated a significantly reduced median number of days to tolerance of clear liquids (0 [range, 0-4] vs 3.0 [2-8], P<.001), days to solid diet (2.0 [1-6] vs 5.0 [3-12], P<.001), and LOS (4.0 [2-8] vs 7.0 [3-14], P<.001) for patients undergoing the laparoscopic procedure compared with open surgery, respectively.[25] Notably, this study also went on to analyze associated costs and found that the mean total costs per patient were $9895 for the laparoscopic group and $13,268 for the open-laparotomy group.

The benefit of a multimodal team approach, as opposed to any single modification of perioperative management practices, was suggested by a recent study, which found that a combination of methods (early feeding, avoidance of NG intubation, and epidural analgesia), rather than a change in surgical technique alone, helped reduce LOS and POI in surgical patients. That is, when a multimodal approach to optimize postoperative outcomes was used, similar improvements in LOS and POI were observed in both the group of patients undergoing open surgery and the set of patients undergoing laparoscopic surgery.[26]

Finer studies of optimal recovery strategies include those of the Controlled Rehabilitation with Early Ambulation and Diet (CREAD) protocol. Developed at the Cleveland Clinic, the CREAD protocol is a planned, fast-track pathway.[3,27] The basic components of the CREAD protocol compared with components of traditional care are shown in **TABLE 2**. As suggested by Basse and colleagues,[26] CREAD—compared with traditional postoperative care—significantly improves outcomes, even in patients undergoing open procedures. In one notable study, patients who received CREAD spent less total time in the hospital after surgery compared with patients who received traditional postoperative care (5.4 vs 7.1 days; P = .01).[27] The researchers also found that

TABLE 2

Components of pathways using CREAD and TRAD

CREAD	TRAD
• PCA only	• NG tube is placed after induction of anesthesia; removed the next day if there is less than 200 mL of drainage over a 4-hour period
• No epidurals are used	• Patients sit out of bed on postoperative day 1
• Ketorolac, 30 mg q 6 h	• Patients are asked to walk 4 to 5 times daily after postoperative day 2
• Orogastric tubes are removed at end of case	• Patients are instructed to take only sips of clear liquid
• Liquids are given the evening of surgery	• Diet is withheld until flatus or stool has passed
• Ambulation on postoperative day 1	• Oral analgesia (oxycodone) is started when liquids are tolerated
• Solid food on postoperative day 1 if liquids are tolerated	• Wall charts are not used
• Oxycodone with discontinuation of PCA on postoperative day 2	
• Wall chart opposite bed for patient to see	

CREAD = controlled rehabilitation with early ambulation and diet; TRAD = traditional postoperative care; PCA = patient-controlled analgesia; NG = nasogastric

Data from Delaney CP, et al. *Dis Colon Rectum*. 2003;46:851-859.

TABLE 3

Brief overview of methylnaltrexone and alvimopan

	Methylnaltrexone	Alvimopan
Pharmacokinetics	Excreted unchanged (approximately 50%) in urine[29]	Excreted primarily via first-pass hepatic metabolism[32]
Phase 3 studies		
• Purpose	To test efficacy for chronic opioid-induced constipation in patients with advanced medical illness*	To test efficacy for POI in patients undergoing colon resection and/or hysterectomy and who were in optimized postoperative recovery ("fast-track") protocols
• Primary efficacy endpoint	Laxation within 4 h of administration of methylnaltrexone	Composite representing recovery of full GI (upper and lower) function (GI-3), the later of: (1) time to toleration of solid food or (2) time to either first flatus or first bowel movement
• Secondary efficacy endpoints	Laxation within 24 h, >3 laxations per wk; adverse events, pain scores, and opioid withdrawal symptoms	Stricter composite representing recovery of GI function: the later of the time to toleration of solid food or the time to first bowel movement (GI-2); readiness for discharge/discharge order written; pain scores, postoperative opioid consumption
Dosing in phase 3 studies†	Initial dose administered subcutaneously (0.15 mg/kg or 0.30 mg/kg); 24 h later, patients eligible to receive open-label methylnaltrexone as needed over next 4 wk	Initial dose administered orally, 30 min-2 h prior to surgery 6 mg or 12 mg, twice daily until hospital discharge, up to a maximum of 7 d[33,34]
Number of patients in completed phase 3 studies	Study MNTX301[30]: N = 154	Study 14CL313[33]: N = 510 Study 14CL302[34]: N = 451 Study 14CL308[35]: N = 666
Number of patients in ongoing phase 3 studies	Study MNTX302[31]: N = 134	Study 14CL306[36]: N = 519 Study 14CL314[37]: N = 660

In phase 3 trials, alvimopan has demonstrated efficacy in reduction of POI in patients receiving opioids for acute perioperative pain. Phase 3 data are not yet available for methylnaltrexone in an analogous perioperative setting; to date, available phase 3 data show a positive effect of methylnaltrexone only in the setting of chronic opioid use by patients with advanced medical illness.

POI = postoperative ileus; GI = gastrointestinal

* See text for phase 2 data on methylnaltrexone for postoperative bowel dysfunction.

† Information regarding dosage and route of administration is from trials published to date.

patients who were treated by surgeons with more experience using the fast-track pathway spent significantly less time in the hospital than did those whose surgeons were less experienced with the pathway ($P = .01$). Furthermore, there was no significant difference between CREAD and TRAD patients with respect to readmission or complication rates, pain score, quality of life after surgery, or overall satisfaction with the hospital stay, indicating that CREAD did not negatively impact these important parameters.[27]

Laparoscopic procedures will certainly play a major role in meeting patients' medical needs because it is clear that in many settings such procedures improve clinical outcomes, shorten LOS, and decrease associated costs. Some debate still surrounds the use of these procedures for certain patients, but compelling evidence attests to the effectiveness of multimodal postoperative care pathways. Inclusion of laparoscopic procedures in the design of these pathways will be crucial to attaining optimal postsurgical outcomes.

However, the potential benefits of laparoscopic surgery need to be balanced with the added considerations

of the specialized instrumentation that is required to use this method, as well as the time and training needed to become proficient with the procedure. In particular, laparoscopic procedures of the colon are more difficult than most standard laparoscopic cases because multiple sites in the abdomen are involved, along with major vascular division. Furthermore, specimen removal is necessary and anastomosis usually is required. Nevertheless, controlled studies have demonstrated benefits to recovery and clinical outcomes using laparoscopic surgery, forcing a reevaluation of many of the dogmatic approaches to POI used in the past. Reviews of studies of the potential benefits of laparoscopy in various surgical settings continue to find an overall reduced duration of POI and associated reductions of approximately 2 days in LOS.[2,28]

Novel pharmacologic approaches

A new class of drugs—peripherally acting mu-opioid-receptor antagonists—may help enhance multimodal management of POI. These drugs accomplish what has eluded researchers for decades: specific activity at gut opioid receptors that blocks the adverse effects of postoperatively administered opioids without inhibiting their centrally mediated analgesic effects. *(See Dr Leslie's article for further details.)* Currently 2 drugs in this new class, methylnaltrexone (MNTX) and alvimopan, are in advanced stages of development. **TABLE 3** provides a brief overview of these 2 drugs.[29-37]

Methylnaltrexone is administered subcutaneously and has been shown to have positive results in phase 3 trials for opioid-induced constipation in patients with advanced medical illness. In MNTX301, a recent phase 3 study of 154 hospice or palliative-care patients, single subcutaneous-injection doses of MNTX, 0.15 mg/kg and 0.30 mg/kg, induced laxation (bowel motility) within 4 hours in 62% and 58%, respectively, of treated patients.[30] The drug was generally safe. It is possible that local (not systemic) opioid withdrawal was responsible for the flatulence and abdominal cramping observed in a substantial number (15% to 40%) of patients, although the authors state that the occurrence of such adverse effects is "consistent" with the drug's mechanism of action. Chronic administration of opioids may lead to altered opioid receptor physiology, resulting in receptor internalization and desensitization.[15,38] In the patient population studied in MNTX301, chronic opioid therapy may have led to gut sensitization; thus, administration of MNTX, an opioid antagonist, may have led to the observed GI symptoms of opioid withdrawal.[39]

In another phase 3 trial (MNTX302), which is currently underway, MNTX is administered once daily over a 2-week period to 134 patients with advanced medical illness.[31] No phase 3 data on the use of MNTX to reduce POI are available at this time, although phase 3 studies to evaluate MNTX for postoperative bowel dysfunction in patients undergoing segmental colectomies are planned.[31]

According to a small phase 2 trial of 65 patients who underwent segmental colectomy, administration of MNTX, 0.3 mg/kg IV every 6 hours for a maximum of 7 days, shortly after surgery accelerates recovery of GI function. Among patients who received MNTX in that study, time to first bowel movement was approximately 95 hours, compared with almost 120 hours for those patients who received placebo.[40] *(See Dr Leslie's article for other details regarding MNTX.)* Reviews to date of MNTX for opioid-induced constipation are available.[41-43]

Alvimopan is administered orally and has been evaluated in large phase 3 trials for the reduction of POI and associated clinical effects. In studies by Delaney's group and Wolff's group, alvimopan was given in twice-daily doses of 12 mg or 6 mg (with the first dose administered at least 2 hours prior to surgery for up to 7 days postsurgery).[33,34] The drug reduced the duration of POI in patients who underwent major abdominal surgery and were recipients of optimized postoperative care. Opioid-mediated analgesia was not compromised and hospital LOS was shortened. Alvimopan was well tolerated and safe; trends in improvement in postoperative nausea also were observed.

Alvimopan received an "approvable" letter from the US Food and Drug Administration in July 2005, and is expected to be available soon in the United States. An ongoing phase 3 trial (study 14CL314) is evaluating alvimopan in bowel resection patients only and at a dose of 12 mg twice daily, with the first dose given 30 to 90 minutes prior to surgery and for a maximum of 7 days following surgery.[37]

To date, use of alvimopan has been evaluated in more than 2100 enrolled subjects undergoing abdominal surgery across 4 phase 3 clinical trials in the United States[37]; final efficacy results are available for 3 of these trials (14CL313, 14CL302, and 14CL308),[33-35] and interim safety results have been presented for the fourth (14CL306, which evaluated the safety of alvimopan in 519 women undergoing total abdominal hysterectomy).[36] Briefly, results observed for studies 306 and 308 were similar to those seen in studies 302 and 313: alvimopan accelerated time to first bowel movement and GI

recovery overall, and exhibited a safety profile similar to placebo. Study 314 is targeted to enroll an additional 660 subjects.[37] *(See also Dr Leslie's article.)* Detailed reviews of alvimopan for POI are available.[9,32,39,44]

Conclusion

It has been suggested that the individual components of multimodal protocols—for example, laparoscopy—may reduce certain postsurgical morbidities (including POI) but do not by themselves prevent POI. Therefore, combinations of strategies with demonstrated effectiveness—early feeding, epidural analgesia, laparoscopic surgery, and use of peripherally acting mu-opioid-receptor antagonists—may help transform the reactive approach to POI into a proactive multimodal paradigm that effectively targets the diverse etiologic factors leading to this common clinical problem. Protocols that incorporate new pharmacologic agents offer yet another avenue for attempts to mitigate the adverse effects of POI, thereby helping improve surgical outcomes.

The author wishes to acknowledge the editorial contributions of Michael Pellegrino, PhD, and the technical assistance of Robert Coover.

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Panel discussion

How were the studies determining the benefits of minimally invasive surgery designed?

Dr Saclarides: One of the problems with the literature on minimally invasive surgery is that not all of the studies were performed in a randomized, prospective way. Instead of taking a group of patients who needed colectomies and randomly assigning half to conventional methods and half to minimally invasive surgery, some study groups performed laparoscopy on consecutive patients and compared the results with those of historical controls. This has given us data that are perhaps not as convincing as they might appear. Additionally, the studies tend to be best-case scenarios in that the laparoscopies have been performed by people who are quite good at the procedure. Not everyone is as familiar with the technique, and not everyone is likely to be able to achieve the same optimal outcomes with it.

Should surgeons come away from this discussion believing that performing minimally invasive surgery is the only way they can prevent postoperative ileus (POI)?

Dr Saclarides: You do the operation that you do best and then consider the other factors that were brought up tonight regarding how to reduce POI: early ambulation, early feedings, efforts to limit use of narcotics and, when we have these drugs that can be used, using them.

Dr Leslie: True, it is certainly not the case that the minimally invasive method is the only useful option. In addition to the factors that Dr Saclarides mentioned, peripherally acting mu-opioid-receptor antagonists show potential to further reduce the duration of POI once they become available. There are avenues available even if it is not possible to perform laparoscopy. I think that ideally it is a part of a multimodal protocol, but if one mode cannot be used, there is no reason why the others still cannot be combined for a significant reduction in duration of ileus.

Does the prospect of reducing POI by what is about 1 day with peripherally acting mu-opioid-receptor antagonists seem significant in light of the fact that POI can last for so many days?

Dr Saclarides: First, let me note something about the studies that found that alvimopan reduces POI by 20 or more hours. The study centers were places that already practiced what we might call the new "gold standard"; they already had procedures in place, such as early removal of nasogastric tubes, early ambulation, and early

feeding, all of which have been shown to reduce POI. If these studies were done routinely all across the United States, most of which does not practice these methods, my belief is that you would see a much more impressive difference made by the drugs. These study centers already had in place a more or less ideal protocol, and I have to suspect that that affected the amount of difference that could be made by further adding the peripherally acting opioid-receptor antagonist.

We also need to look at discharge patterns because they depend in part on when doctors make their rounds. We would probably have a more accurate picture of recovery time if the studies recorded the time at which the patient met discharge criteria, no matter what time of the day or night, but of course it does not work that way. Functionally, because of discharge patterns, any time over 12 hours meeting discharge criteria ends up amounting to an extra day in the hospital. Furthermore, the economic burden of these extended stays can vary; low-volume institutions may be able to close a nursing unit when patients are discharged earlier, and high-volume institutions can probably use the bed for another patient; it may not be as clear of an economic case if your institution is somewhere in between. However, 20 hours can easily amount to a very substantial cost if, for instance, you have patients waiting in the recovery room who cannot get to beds upstairs and stay in the postanesthesia care unit where there is full-time one-on-one nursing.

What would be the downside of simply eliminating all postoperative use of opioids and using nonsteroidal anti-inflammatory drugs (NSAIDs) like ketorolac tromethamine universally?

Dr Wolff: Well, that's what they often do in Europe.

Dr Leslie: Yes, either we simply are not as tough over here or our surgeries are just a little more invasive. I believe ketorolac tromethamine just doesn't provide enough pain protection for a major laparotomy. This is true with other NSAIDs and cyclooxygenase-2 inhibitors as well; narcotics are still necessary for breakthrough pain. In the United States, with the new recommendations from the Joint Commission on Accreditation of Healthcare Organizations, we need to keep pain-scale scores under 4, and to achieve this, it is often necessary to administer patient-controlled analgesia on top of the other pain medication. It becomes a complicated group of several drugs all used in an effort to keep the opioid load down. Of course, these alternatives are not without their own risks. Ketorolac tromethamine really should not be given to elderly patients, it carries the risk of reduced kidney function, and there are some bleeding issues. For a variety of reasons, I can't see postoperative opioids being abandoned in the United States any time soon.

Integrating new agents for postoperative ileus into multimodal protocols

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For each of the following questions, please circle the best response.

1. **Postoperative ileus (POI) can be associated with which of the following procedures:**
   A. Arthroplasty
   B. Thoracic surgery
   C. Hysterectomy
   D. All of the above

2. **Clinical presentation of POI often differs from patient to patient. Which of the following is *not* generally found in patients with POI?**
   A. Bloating
   B. Increased blood urea nitrogen and creatinine
   C. Nausea and/or vomiting
   D. Inability to pass stool

3. **The most common cause of POI is:**
   A. Trauma and manipulation of the bowel
   B. Release of endogenous endorphins
   C. Stimulation of somatic and visceral fibers
   D. Anesthetic and postoperative pain medications

4. **The duration of POI is proportional to:**
   A. Exposure and dose of opioid analgesia
   B. Intra-abdominal manipulation
   C. Use of nasogastric intubation
   D. Initiation of postoperative feeding

5. **Which of the following statements about the new opioid-receptor antagonists is correct?**
   A. They do not pass the blood-brain barrier
   B. They minimize pain management
   C. They minimize blood pressure changes associated with use of opioids
   D. They hydrate the stool for better motility in the bowel

6. **The gastrointestinal-selective opioid-receptor antagonists may help shorten the duration of POI without compromising pain management.**
   A. True
   B. False

7. **Multimodal protocols for management of POI are likely to include all of the following except:**
   A. Laxatives
   B. Laparoscopic procedures
   C. Early feeding
   D. None of the above

8. **For every patient who may need nasogastric intubation, there are ____ patients who do not.**
   A. 10
   B. 20
   C. 30
   D. 40

9. **Early feeding may shorten the duration of POI and hospital stay following select surgeries. With which of the following procedures does this *not* appear to be true?**
   A. Thoracic surgery
   B. Gastrectomy
   C. Colonic surgery
   D. Gynecologic surgery

10. **Which of the following statements about epidurals is false?**
    A. They are associated with fewer pulmonary complications
    B. They decrease blood loss
    C. They improve pain control
    D. They facilitate mobility

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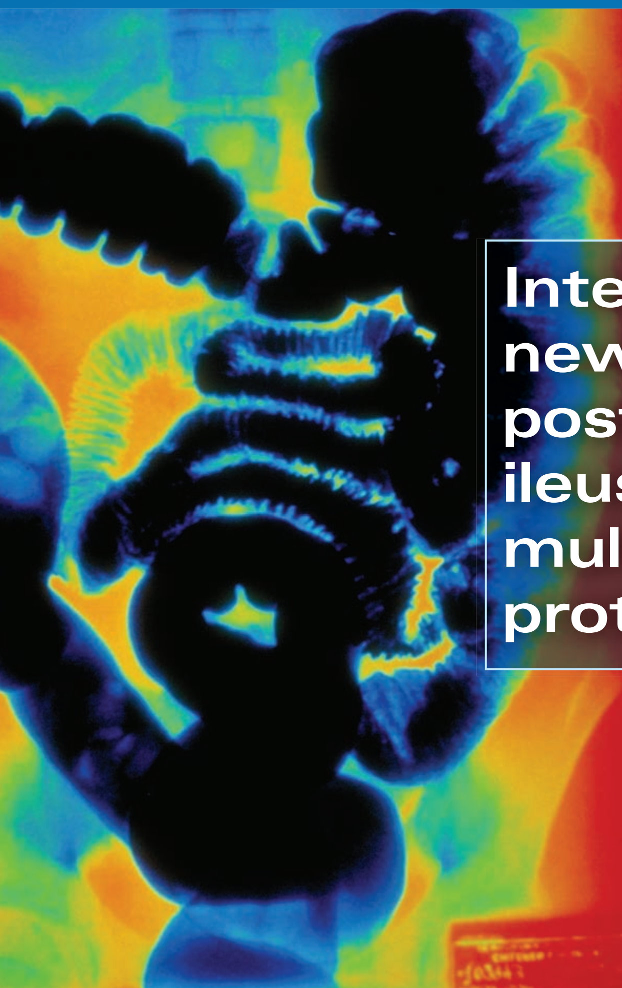

Integrating new agents for postoperative ileus into multimodal protocols

This program is jointly sponsored by the University of Cincinnati College of Medicine and Dowden Health Media, and is supported by an unrestricted educational grant from Adolor Corporation and GlaxoSmithKline.