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Ghrelin Agonist TZP-101/Ulimorelin Accelerates Gastrointestinal Recovery Independently of Opioid Use and Surgery Type: Covariate Analysis of Phase 2 Data

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Abstract
Background Delayed recovery of gastrointestinal (GI) motility is a common complication following surgery. TZP-101/ulimorelin is a macrocyclic peptidomimetic ghrelin receptor agonist with GI promotility effects that significantly accelerates time to recovery of GI motility compared to placebo following partial colectomy. It is also well tolerated. The objectives of this analysis were to identify predictors of GI motility recovery in patients undergoing partial colectomy and to evaluate whether these factors affect ulimorelin acceleration of GI recovery.
Methods Covariate analysis assessed the effect of eight variables—age, sex, body mass index, type of surgery (right colectomy, left colectomy, other), duration of surgery, blood loss, total opioid consumption, country—on recovery of GI motility in 236 patients randomized to ulimorelin ($n = 168$) or placebo ($n = 68$). The primary endpoint was the recovery of GI function (time from the end of surgery to first bowel movement). Stepwise regression identified a parsimonious model of the smallest subset of variables best predicting GI recovery.
Results Recovery was shorter for segmental/subtotal colectomies vs. right colectomies ($P = 0.016$) and longer with increased total opioid use ($P = 0.037$). The remaining variables had no statistically significant effect on GI recovery. Effects of ulimorelin 480 μg/kg (the most effective dose) on time to GI tract recovery remained statistically and clinically significant (hazard ratio = 1.81, $P = 0.014$) when adjusted for surgery type and/or total opioid use.
Conclusions Two factors, type of surgery and total opioid use, independently modified times to recovery of GI motility following partial large bowel resection surgery. Acceleration of recovery of GI motility by ulimorelin was independent of these factors.

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Introduction

Delayed recovery of gastrointestinal (GI) motility is common after surgery. It contributes to patient morbidity and discomfort [1] and to increased health care costs [2]. Potential factors contributing to delayed recovery of GI motility include physiological responses to surgical trauma (e.g., endocrine responses; elaboration of endogenous opioids and inflammatory cytokines [3]) as well as factors related to perioperative care, such as general anesthesia and opioid use [4]. Although the causative factor of delayed GI recovery is the surgical procedure itself, the delay is often exacerbated by perioperative opioid use. Opioid-based regimens are common treatments for postsurgical pain management; however, opioids bind to mu receptors in the gut and can prolong the duration of GI recovery through delayed gastric emptying, reduced GI motility, and disrupted colonic myoelectric activity [5].

In addition, increased duration of surgery and blood loss have been identified as risk factors for prolonged recovery of GI motility following abdominal surgery [6]. In a cohort

of 283 patients who underwent radical cystectomy, delayed GI recovery occurred in 15.2%. The demographic factors age and body mass index (BMI) were significantly associated with its incidence, whereas intraoperative features (e.g., estimated blood loss, operating time, surgeon of record) were not [7]. Similarly, Pikarsky et al. observed an increased incidence of delayed GI recovery in obese patients undergoing laparoscopic colorectal surgery versus normal-weight patients [8]. The identification of any additional risk factors for delayed GI recovery following surgery is relevant as it is currently not possible to predict which patients will experience prolonged recovery of GI motility following surgery.

Current strategies to accelerate recovery of GI motility are aimed at "fast-track" or "enhanced-recovery" protocols designed to reduce the impact of external and internal factors on delayed GI function [9, 10]. The goal of these protocols is to enable patients to recover earlier and therefore go home sooner after surgery. A meta-analysis of randomized controlled trials showed that fast-track protocols can reduce the length of primary hospital stays [11]. However, data pooled from placebo arms of clinical trials indicate that 34% of patients undergoing partial bowel resection as part of standardized accelerated care pathways were discharged from the hospital $\geq$7 days after surgery, and more than 9% required a prolonged hospital stay or readmission [12]. A 2008 Cochrane review concluded that most drugs routinely used to enhance bowel recovery after major abdominal surgery are not supported by current research evidence [13], and an unmet need for effective treatment remains.

Ulimorelin, a macrocyclic peptidomimetic ghrelin receptor agonist with GI promotility effects, is in clinical development for GI dysmotility disorders [14–19]. Ghrelin is the natural ligand for growth hormone secretagogue receptors (GHSR-1a), and both ghrelin and GHSR-1a are co-localized in the proximal GI tract [20]. The ghrelin receptor pathway mediates multiple GI functions, including motility, gastric emptying, and induction of migrating motor complexes (MMCs) [21]. This macrocyclic compound represents the first of a new class of ghrelin agonists that does not duplicate any portion of the sequence of ghrelin. Ulimorelin has enhanced metabolic stability and high affinity (K_i 22 nM) for the human type 1a GHSR compared to ghrelin [22]. It has shown promotility activity in animal models of GI dysmotility [14, 15] and in patients with gastroparesis [16, 18].

Ulimorelin is well tolerated in healthy subjects and in gastroparesis and postsurgical patients when administered in daily doses ranging from 20 to 600 μg/kg [16–19]. Patients treated with ulimorelin doses of 20 to 600 μg/kg following partial colectomy had significantly accelerated times to recovery of GI motility in all dose groups by 10–22 h versus placebo. Also, more patients who received ulimorelin achieved recovery by 72 hours after surgery compared to those given a placebo, resulting in an accelerated median time to readiness for hospital discharge compared with the placebo group [19]. Based on the results of this multicenter study in 236 patients undergoing treatment, the most effective ulimorelin dose was identified as 480 μg/kg.[19] The two most common treatment-emergent adverse events, nausea and vomiting, were reduced in the ulimorelin group compared with the placebo group [19].

The first objective of the present analysis was to identify predictors of recovery of GI motility in patients undergoing partial colectomy. The second aim was to evaluate whether these factors affected ulimorelin acceleration of GI recovery.

Methods

A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study was conducted from July 2007 to July 2008 at 29 sites: seven in the United States, nine in Romania, nine in India, and four in Lithuania (Clinical Trial Registry #NCT00617552). A full description of the study methods and primary results has been previously published [19]. The patients included were adult (18–80 years) men and women with body weights $\leq$100 kg scheduled to undergo open partial colectomy with primary anastomosis, including segmental colon resection, right or left hemicolectomy and subtotal colectomy. Patients were scheduled to have available postoperative pain management with intravenous opioids (including patient-controlled analgesia) and enhanced-recovery, or "fast-track," postoperative care that included removal of the nasogastric tube at the end of surgery, oral liquids and ambulation encouraged on postoperative day (POD) 1, and solid food offered on POD 2. To obtain a relatively homogeneous patient population, patients undergoing colostomy or ileostomy creation, total colectomy, low anterior resection, surgery for complete bowel obstruction, and laparoscopic procedures were excluded [19].

Ulimorelin (20, 40, 80, 160, 320, 480, and 600 μg/kg) or placebo was administered by intravenous infusion beginning within 1 h after surgery and continued on a daily basis until the first bowel movement, hospital discharge, or POD 7, whichever came first as previously described [19]. Internet-based or interactive voice response systems were used for randomizing the first 100 eligible patients in equal numbers to receive daily intravenous infusions (60 ml/30 min) of matching placebo or ulimorelin (20, 40, 80, 160, 320, 480, and 600 μg/kg) beginning within 1 h of the conclusion of surgery. Subsequent participants were assigned to treatment groups using an adaptive

randomization scheme with prospectively defined allocation and decision rules. On a weekly basis, available study data (time to first bowel movement) were used to generate a new randomization vector to determine dose allocation for the next group of patients.

The primary endpoint was the recovery of GI function defined as the time from the end of surgery to first bowel movement ("GI"). A secondary endpoint ("GI2") was recovery of GI function defined by the time from the end of surgery to the later of the following two events: (1) time that the patient first tolerated solid food and (2) time that the patient first had a bowel movement—thereby evaluating both upper and lower GI recovery.

For this analysis, the potential effect of eight variables—age, sex, body mass index (BMI), type of surgery (right, left, other), duration of surgery (in hours), blood loss, total opioid consumption, country—on postsurgical recovery of GI motility in patients receiving ulimorelin versus placebo was considered. Initially, stepwise proportional-hazard regression was used to identify parsimonious models of GI tract recovery (a parsimonious model is one where the smallest subset of variables adequately predicts the GI recovery endpoints) across the total study population. Subsequently, to determine whether any or all of these variables influenced the effect of ulimorelin on recovery of GI motility, covariate analysis was used to assess the "GI" and "GI2" endpoint data (Cox proportional hazards model) for the ulimorelin dose groups versus placebo. The Wald test was used to calculate *P* values for the hazard ratios (HRs) of individual ulimorelin dose levels relative to placebo and for the overall significance of the differences among all dose groups.

With respect to sample size, in Bayesian adaptively randomized studies such as this one sample sizes can only be estimated in advance, as the ongoing results determine the final number of patients enrolled in the study. This study included a predefined weekly automated Bayesian analysis to determine the best performing doses and define new weekly randomization schemes. Complete details are described elsewhere [19].

Previous reporting of the primary endpoints from this study identified the 480 μg/kg dose of ulimorelin as the most effective one for improving recovery of GI motility [19]. Therefore, results are presented for this dose relative to placebo. Safety data for this study have been previously analyzed and reported [19]. Adverse events occurring in the placebo and the ulimorelin 480 μg/kg dose groups are briefly summarized in this report.

Results

A total of 236 randomized patients were dosed in the United States (19 patients), Romania (129 patients), India (75 patients), and Lithuania (13 patients). In all, 68 patients received placebo and 168 patients received ulimorelin. Treatment groups were similar with respect to demographic and baseline surgery characteristics (Table 1) with the exception that a larger proportion of patients receiving any ulimorelin dose were male (60%) compared to patients receiving placebo (44%). The surgical resection procedures performed were predominantly right hemicolectomy (106/236, 45%), segmental colon resection (75/236, 32%), and left hemicolectomy (44/236, 19%).

Total opioid [calculated as morphine equivalents (MEs)] use per patient ($n = 236$) organized by country is shown in Fig. 1. The total opioid use ranges were broad. The medians (ranges) of total opioid use by patients receiving

Table 1 Summary demographics and baseline characteristics

Parameter	Placebo ($n = 68$)	All ulimorelin doses ($n = 168$)	Ulimorelin 480 μg/kg ($n = 25$)
Age (years), mean ± SD	55 ± 16	59 ± 15	60 ± 14
Sex (no.) (%)			
Male	30 (44%)	101 (60%)	11 (44%)
Female	38 (56%)	67 (40%)	14 (56%)
Race (no.)			
Asian	26 (38%)	48 (29%)	8 (32%)
African American	0	1 (0.6%)	0
White	42 (62%)	118 (70%)	17 (68%)
Other	0	1 (0.6%)	0
BMI (kg/m^2), mean ± SD	24.3 ± 4.07	23.9 ± 4.82	23.5 ± 4.97
Surgery duration (h), mean ± SD	2.5 ± 0.91	2.6 ± 1.08	2.5 ± 0.98
Anesthesia duration (h), mean ± SD	3.03 ± 1.04	3.13 ± 1.16	3.05 ± 1.08
Blood loss (ml), mean ± SD	243.43 ± 232.56	244.64 ± 202.22	258.4 ± 214.02

BMI body mass index

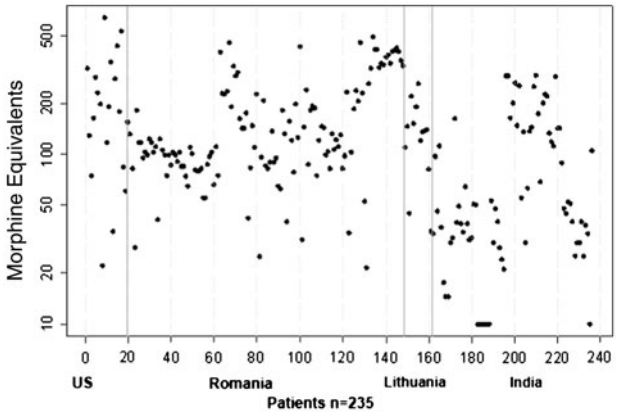

Fig. 1 Total opioid use in morphine equivalents per patient organized by country. Number of patients: United States, $n = 19$; Romania; $n = 129$; Lithuania, $n = 13$; India, $n = 75$

ulimorelin in the United States, Romania, Lithuania, and India, respectively, were 170.8 (35–636.1), 104 (28–495), 136.2 (35–220), and 51.1 (10–289) MEs.

In an analysis of the entire study population, including all doses and placebo ($n = 236$), two variables were identified in the stepwise regression parsimonious model (i.e., the model identifying the fewest covariates best predicting GI recovery). Their effects on recovery of GI motility following partial large bowel resection surgery are shown in Table 2. These two variables, surgery type and total opioid use, had statistically significant effects on both "GI" and "GI2" across the entire study population. The results indicate that "GI" was significantly shorter for patients who underwent segmental or subtotal colectomy than for those with a right hemicolectomy ($P = 0.016$). Also, the "GI" was slightly longer with increased total opioid use: For each additional 10 ME of opioids used, recovery was delayed by 1% ($P = 0.037$). Similarly "GI2" was significantly shorter for segmental and subtotal colectomies than for right hemicolectomy ($P = 0.044$). Also, "GI2" was slightly longer with increased total opioid use: For each additional 10 ME of opioids used, recovery was delayed by 1% ($P = 0.007$). The effects of the remaining six variables on GI recovery were not statistically significant in this analysis of the 236 patients.

Cox proportional hazard models for unadjusted and variable-adjusted ulimorelin 480 μg/kg dose effects on GI recovery are shown for "GI" and "GI2" endpoints in Table 3. The first row shows the hazard ratios and p values for ulimorelin acceleration of GI recovery without adjustment for any variable. As indicated in the Table 3, ulimorelin acceleration of GI recovery remained significant when adjusted for individual covariates for "GI" and all but opioid use for "GI2" (although results trended toward significance) and when adjusting for all covariates. The effects of adjusting for the two covariates identified in the parsimonious model are shown in the last row of Table 3. For "GI", the adjusted hazard ratio is numerically larger and more significant (HR = 1.81, $P = 0.014$) than the unadjusted hazard ratios. For "GI2", the value of the adjusted hazard ratio is the same as the unadjusted hazard ratio (1.61) and approaches significance ($P = 0.06$). Figure 2 summarizes the shifts in hazard ratios when adjusted for variables identified from the parsimonious model.

Table 2 Effect of variables identified from stepwise proportional-hazards regression (parsimonious model) across the total study population ($n = 236$)

Covariate	Recovery measure	Effect	P
Surgery type	"GI"	Shorter for segmental/subtotal versus right	0.016
	"GI2"		0.044
Total opioid use	"GI"	Longer with increased opioid use	0.037
	"GI2"		0.007

"*GI*" primary endpoint; "*GI2*" secondary endpoint

Safety

Treatment emergent adverse events for the placebo and ulimorelin 480 μg/kg group, shown in Table 4, are similar to those previously reported for all the ulimorelin doses combined [19]. Overall, the incidence of events was lower

Table 3 Effect of adjusting for variables, individually and combined, on the ulimorelin impact on recovery of GI motility

Covariate	"GI" HR	"GI2" HR
Without adjustment for any covariates	1.67 (0.029)[a]	1.61 (0.044)
Country	1.63 (0.044)	1.61 (0.050)
Sex	1.70 (0.026)	1.64 (0.037)
Age	1.71 (0.027)	1.66 (0.037)
Weight	1.68 (0.028)	1.64 (0.038)
Duration of surgery	1.70 (0.024)	1.60 (0.048)
Blood loss	1.71 (0.025)	1.61 (0.047)
Surgery type	1.83 (0.012)	1.83 (0.013)
Total opioid use	1.63 (0.038)	1.56 (0.061)
Adjustment for all covariates combined	1.73 (0.036)	1.67 (0.051)
Adjustment for two covariates identified in parsimonious model: total opioids and surgery type	1.81 (0.014)	1.61 (0.06)

Results are the hazard ratios for ulimorelin 480 μg/kg dose ($n = 25$) versus placebo ($n = 69$) for the "GI" and "GI2" endpoints. *HR* hazard ratio

[a] Numbers in parentheses are the p values

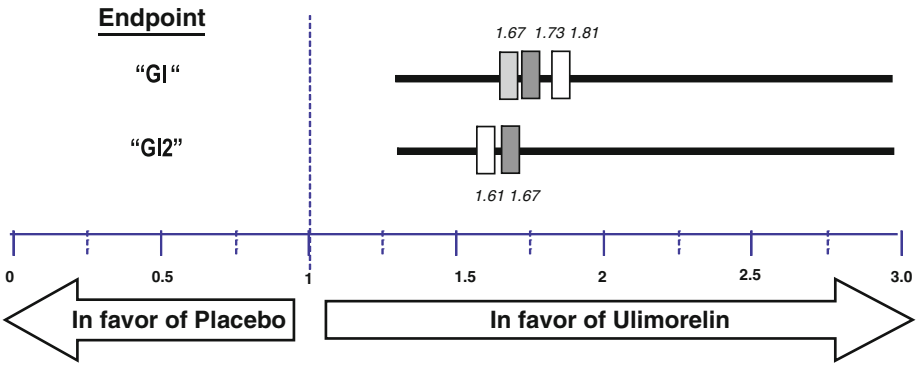

Fig. 2 Ulimorelin (480 μg/kg) (*TZP-101*) effects on gastrointestinal (GI) recovery. Hazard ratios and confidence intervals adjusted for parsimonious model (*white bars*). For comparison, unadjusted (*light gray bars*) and all adjustment (*dark gray bars*) hazard ratios are shown. *"GI"*: primary endpoint; *"GI2"*: secondary endpoint. Note that for "GI2," the unadjusted and parsimonious models are both 1.61

in the ulimorelin group (32%) than in the placebo group (57%). Nausea and vomiting occurred frequently in the placebo group but not in the ulimorelin group. Previous reporting of safety data for the entire study that showed time-averaged analysis of change from baseline for the heart rate, PR interval, QRS, QT, and QTcB did not identify dose-dependent changes or notable differences from placebo [19]. Clinical or laboratory evaluations showed no clinically relevant differences between ulimorelin and placebo-treated patients.

Table 4 Treatment emergent adverse events occurring in ≥3% of patients in the placebo and ulimorelin 480 μg/kg groups

Adverse event	Placebo ($n = 68$)	Ulimorelin 480 μg/kg ($n = 25$)
Patients with at least one TEAE	39 (57.4%)	8 (32.0%)
Nausea	18 (26.5%)	1 (4.0%)
Vomiting	11 (16.2%)	1 (4.0%)
Pyrexia	4 (5.8%)	0
Wound infection	3 (4.4%)	2 (8.0%)
Hypoalbuminemia	3 (4.4%)	0
Urinary tract infection	3 (4.4%)	0
Hypertension	2 (2.9%)	2 (8.0%)
Hyperglycemia	1 (1.5%)	1 (4.0%)
γ-Glutamyltransferase increase	4 (5.9%)	0
Alanine aminotransferase increase	4 (5.9%)	1 (4.0%)
Aspartate aminotransferase increase	4 (5.9%)	1 (4.0%)
Hypoproteinemia	3 (4.4%)	0

TEAE treatment emergent adverse events

Discussion

Delayed recovery of GI motility following abdominal surgery is a common occurrence. It is thought to involve neural pathways, chemical mediators that vary depending on the portion of the GI tract involved, and inflammatory responses [23]. Identified risk factors for delayed recovery of GI motility following surgery include opioid use and more-invasive surgical procedures, but independent predictors of delayed GI tract recovery in patients have not been well studied. A recent study identified the amount of blood loss and total surgical time as independent predictors of delayed recovery of GI motility following abdominal surgery [6]. In this study, we examined potential predictors of delayed recovery of GI motility in patients undergoing partial colectomy and then assessed the efficacy of the ghrelin agonist ulimorelin when recovery times were adjusted for the effects of these predictors.

Ulimorelin has previously been shown to have promotility effects in patients with delayed GI motility, including diabetes-associated gastroparesis [16, 18] and in patients recovering from a partial colectomy [19]. Recovery of GI motility after surgery can be delayed because of dysmotility of the stomach or the small or large intestine. It has generally been thought that the small bowel normally resumes activity several hours after surgery, the stomach 24–48 h after surgery, and the colon 3–5 days after surgery [24].

Ghrelin has potent promotility action [21]. It has also been shown to activate a cholinergic antiinflammatory pathway, and this pathway may be a useful target in preventing inflammatory cascades associated with postoperative ileus [25]. Therefore, both the promotility and antiinflammatory effects of ghrelin agonists may contribute to recovery of GI motility after abdominal surgery. The ghrelin agonist ulimorelin may have advantages over peripheral opioid antagonists used in the management of postoperative ileus (POI) as well as over other agents used for dysmotility including erythromycin, dopamine antagonists, and cholecystokinin agonists, which have shown lack

of evidence or absence of effective improvement in recovery of GI tract motility after abdominal surgery [13].

Patients in the study undergoing partial colectomy received enhanced-recovery, or "fast-track," postoperative care that included removal of nasogastric tubes at the end of surgery, oral liquids, and ambulation encouraged on POD 1, and solid food offered on POD 2. Under these conditions, median times to "GI" and "GI2" in the placebo group were 90 and 91 h, respectively ($\sim$4 days), as previously reported [19]. Ulimorelin (480 μg/kg) improved these times by 22 and 23 h, respectively, or by almost a full day [19].

In the present analysis, eight variables were assessed to determine whether they were factors that influenced recovery of GI motility in postsurgical patients. A stepwise regression algorithm was run, and the variables were selected by a stepwise algorithm as the most "parsimonious" model (i.e., the model with the fewest terms needed, in the sense that adding any extra covariates would not make the model substantially better but removing any of the selected covariates would make the model substantially worse). For the "GI" endpoint, the type of surgery and total opioid use were the best predictors: Segmental and subtotal colectomies were associated with shorter recovery times relative to right partial colectomy; and greater total opioid use was associated with longer recovery times. Similar associations were identified for "GI2", indicating that recovery of both upper and lower GI functions were similarly affected.

With the variables most influencing recovery time identified, the regression analysis for the effect of ulimorelin on "GI" and "GI2" was adjusted for the effect of these variables. Ulimorelin remained effective in decreasing recovery times independent of the effect of the influencing covariates. When the model was adjusted for the parsimonious variables that decreased (surgery type) or increased recovery time (total opioid use), ulimorelin had a greater numerical effect on time to recovery of the "GI" endpoint and greater statistical significance than when unadjusted for these two variables, whereas time to recovery for "GI2" was unchanged.

We cannot conclude from our study that the duration of surgery and blood loss were factors in recovery of GI motility in the patient population studied, although there was little variability in the duration of surgery or the amount of blood lost. Segmental and subtotal colectomies were associated with shorter recovery times than right colectomy, with the recovery times for right and left colectomies not statistically different. Not surprisingly, total opioid use correlated with increased delay of GI recovery: For each additional 10 ME of opioids used, GI recovery was delayed by 1%.

Pharmacologic approaches to improving GI recovery after surgery are limited [13]. Entereg is a peripherally acting mu opioid antagonist approved in the United States for accelerating GI recovery following partial large or small bowel resection surgery with primary anastomosis. Entereg did not show clinically significant acceleration of recovery in a study based in Europe, where patient-controlled analgesia is not used as commonly as in the United States [26]. In contrast, the mechanism of action of ulimorelin is opioid-independent. Patients in the present study were enrolled in the United States, Europe, and Asia and received a range of parenteral opioid doses (including some via patient-controlled analgesia). Ulimorelin-related improvements in GI tract recovery times persisted when adjusted for opioid use, indicating that ulimorelin should remain effective in improving time to recovery of GI motility even when enhanced-recovery and opioid-sparing pain management protocols are used.

Ulimorelin has a good safety and tolerability profile in patients with GI tract dysmotility [16, 18, 19]. In the present analysis, safety profiles in the placebo and ulimorelin group were consistent with those of other patients undergoing abdominal surgery. Nausea and vomiting, which were the most common treatment-related adverse events in the placebo group, did not occur in patients receiving the 480 μg/kg dose of ulimorelin.

Conclusions

This analysis identified two factors, type of surgery and total opioid use, that independently modified times to recovery of GI motility following partial large bowel resection surgery. Additionally, the acceleration of recovery of GI motility by ulimorelin was independent of these factors. The observation that opioid use did not have a substantial impact on the effect of ulimorelin underscores the opioid-independent mechanism of this GI promotility agent and the potential utility of ulimorelin in surgical GI recovery protocols that minimize opioid use.

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