

Diagnosis, Characterization, and 3-Month Outcome After Detoxification of 39 Patients With Narcotic Bowel Syndrome

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- OBJECTIVES:** Narcotic bowel syndrome (NBS) is characterized by a paradoxical increase in abdominal pain associated with continued or escalating dosages of narcotics. This study evaluated the clinical and psychosocial features of patients with NBS and the response to detoxification treatment.
- METHODS:** For 2 years, 39 patients seen by the GI consult service at the University of North Carolina at Chapel Hill (UNC) with presumed NBS were placed on a detoxification program. Clinical, psychosocial, health status, and outcome data were obtained before and after detoxification. Our aims were to: (i) clinically characterize patients with presumed NBS, (ii) assess the clinical response and adverse effects to detoxification, (iii) identify clinical and psychosocial predictors of treatment response, and (iv) determine the clinical outcome at 3 months after detoxification and the time frame for patients who revert back to narcotics.
- RESULTS:** Of the 39 patients detoxified, 89.7% met predefined criteria. Patients were mostly well educated (14.5±2.3 years of school), female (92.3%), and with a variety of diagnoses (21% irritable bowel syndrome IBS/functional, 37% inflammatory bowel disease and other structural, 29% fibromyalgia and other functional somatic, or orthopedic, and 13% postoperative or other). They reported high health-care use (15.3±10.1 MD visits/6 months; 6.5±6.1 hospitalizations/2 years, 6.4±2.0 surgeries/lifetime), and 82.1% were jobless. Despite high dosages of narcotics (total intravenous (IV) morphine equivalent 75.3±78.0 mg/day), pain scores were rated severe (52.9±28.8 visual analog scale (VAS); 257.1±139.6 functional bowel disorder severity index (FBDSI); 17.2±10.2 (McGill Pain and greater than labor or postoperative pain). Multiple symptoms were reported ($n=17.8±9.2$) and rated as moderate to severe. Psychosocial scores showed high catastrophizing (19.9±8.6); poor daily function (Short Form-36 (SF-36) physical 28.3±7.7, mental 34.3±11.0; worse than tetraplegia); 28.2% were clinically depressed and 33.3% anxious (Hospital Anxiety and Depression Scale (HADS)). Detoxification was successfully completed by 89.7%; after detoxification, abdominal pain was reduced by 35% ($P<0.03$) and nonabdominal pain by 42% ($P<0.01$) on VAS, and catastrophizing significantly improved ($P<0.01$). Responder status was met in 56.4% with 48.7% achieving a ≥30% reduction in pain. By 3 months after detoxification, 45.8% had returned to using narcotics. For those who remained off narcotics at 3 months, the VAS abdominal pain score was 75% lower than pretreatment when compared with those who went back on narcotics (24% lower). Successful detoxification and a good clinical response was associated with low abuse potential (Current Opioid Misuse Measure (COMM) score <9).

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Received 8 February 2012; accepted 23 April 2012

CONCLUSIONS: Despite severe pain, poor coping, and poor health status, almost all patients with NBS undergoing detoxification were able to stop using narcotics and have significant improvement in pain and coping. However, almost ½ reverted to narcotic use at 3 months. Those who stayed off narcotics showed greater improvement in pain scores. This study provides a rationale for treating patients with NBS by detoxification in order to improve their clinical status. Further work is needed to understand the reasons for the high recidivism rate.

Am J Gastroenterol advance online publication, 19 June 2012; doi:10.1038/ajg.2012.142

INTRODUCTION

Narcotic bowel syndrome (NBS) is characterized by a paradoxical increase in abdominal pain associated with continuous or increasing dosages of narcotics (1). It is less common than, but may be associated with, opioid bowel disorder, which is a dose-related dysmotility leading to constipation, gastroparesis, or ileus. Although originally reported over two decades ago (2,3), NBS is becoming increasingly recognized, possibly because of an increase over the last decade in narcotic prescribing for chronic nonmalignant conditions (1). Although initially narcotics relieve the pain, with continued use, a subset (by one estimate ~6%) (4) of patients taking narcotics chronically go on to develop NBS. Patients with NBS first develop tolerance or tachyphylaxis, and then hyperalgesia, even with dose escalation. NBS is not associated with any particular medical condition, and occurs in patients with a variety of disorders or when treated with high-dose narcotics postoperatively. Because increasing numbers of patients taking high doses of narcotics are being hospitalized or referred to gastroenterologists, it becomes important to recognize this condition and find ways to treat it.

Since the publication of our NBS case series over 4 years ago (1), we have continued to identify, characterize, and treat this disorder. We now report a prospective study of patients presumptively diagnosed with NBS who were treated with detoxification. Our aims were to: (i) characterize patients with regard to medical comorbidities, clinical features, diagnosis using NBS criteria, health-care utilization, and medications used; (ii) assess the clinical response and adverse effects to detoxification and associated medication treatments; (iii) identify clinical and psychosocial baseline predictors of treatment response; and (iv) determine the clinical outcome at 3 months after detoxification and the time frame for patients who revert back to narcotics.

METHODS

Population sample and recruitment

Between November 2008 and November 2011, we identified male and female adult patients with severe chronic abdominal pain who were taking narcotics. The patients were seen as referrals to the outpatient service of the Functional GI Clinic of the University of North Carolina at Chapel Hill (UNC) Center for Functional GI and Motility Disorders or the general gastroenterology clinic in the Division of Gastroenterology and Hepatology at UNC. If the treatment team determined that the patient's abdominal pain was not responding to chronic or high dosages of

narcotics and the patient was willing to undergo detoxification, he or she was entered into the study. If inpatient detoxification was selected, patients were usually started on an antidepressant and hospitalization for detoxification was scheduled usually within 2 weeks. For hospitalized patients, the GI fellow usually discussed the option of entering the study, and for clinic patients the treating physician would request permission. If the patient agreed, the research assistant greeted the patient and reviewed and signed the consent form and helped the patient fill out questionnaires either in the hospital or for outpatients during the clinic visit. This study was observational with no required protocol; however, the GI team was familiar with the detoxification protocol (see Appendix) and usually made recommendations for treatment based on this document. In the hospital the patient was seen frequently by the GI consultation service, the research assistant, and often by the Functional GI Program psychologist. Outpatients undergoing detoxification were seen primarily by the treating physician with frequent phone calls by the research assistant. This study was approved by the institutional review board at UNC.

Questionnaire administration

After signing informed consent the patient completed a battery of questionnaires as noted below:

Initial assessment. The patients completed: (i) *Demographic and Medical Form* that included age, gender, marital status, education, as well as items relating to current health, diagnosis based on Rome III criteria, health-care utilization, and pain scores using Visual Analog Scale (VAS) and Likert scale; (ii) The *Functional Bowel Disorder Severity Index (FBDSI)* (5) is a validated instrument that was used to assess abdominal pain severity; (iii) a single *Diary Card* was given to collect data that contained: *McGill pain Questionnaire* (6,7), stool frequency and consistency using the *Bristol Stool Form Scale* (8), stress level, and medications; (iv) The *Clinical Questionnaire* for NBS was developed by our group to obtain information before and just after detoxification. It contained questions about additional medical diagnoses, the types and dosages of narcotics used before detoxification, contact information of referring and managing physicians, whether detoxification was done as inpatient or outpatient and whether it was completed, the specifics of the detoxification with medications used daily and the response to withdrawal, side effects, requests to modify or negotiate the withdrawal, and the medications used after detoxification; (v) *Psychosocial questionnaires* included the Catastrophizing subscale of the *Coping Strategies Questionnaire* along with two questions on the ability to decrease or control symptoms (coping) (9), the

IBS-QOL (condition-specific health-related quality of life) (10,11), the *Short Form-36 (SF-36)* (12) (generic measure of daily function and quality of life), the *Symptom Checklist-90 (SCL-90)* (13) (psychological state measure), *Hospital Anxiety and Depression Scale (HADS)* (14) (anxiety and depression), *Sexual and Physical Abuse* (15), and the *Medical Symptom Inventory (MSI)*, a checklist of 56 somatic symptoms scored on severity using a 5-point Likert scale; (vi) the *Current Opioid Misuse Measure (COMM)* (16) assesses the likelihood of substance abuse potential. The Items relate addiction-prone behaviors (“how often have you had to borrow pain medication from someone else”), emotional lability (“how often have you been in an argument”), and dysphoria (“how often have you seriously thought about hurting yourself”) that could relate to a poor outcome. A cutoff of ≥ 9 has been shown to have high negative predictive value. A high score has ~33% false positives but a low score has very few false negatives.

End of Treatment Assessment (after detoxification). After the patient was completely detoxified and usually on the day of discharge, the research assistant reviewed the hospital records and assessed treatment response. Patients received: (i) *Clinical Questionnaire for NBS*; (ii) *Diary card* (degree of pain reduction); (iii) *Psychosocial Questionnaires* including catastrophizing and ability to decrease and control symptoms, *HADS*, and *SCL-90*; (iv) *Clinical Outcome* that included questions on whether the patient was off narcotics, qualitative questions about addiction proneness and related questions, and pain scores and responder measures. The primary assessment measure was (i) the VAS (0–100 mm VAS) with a 30% reduction before and after treatment and at 3 months. We also looked at other standard measures of outcome: (ii) *adequate relief* (y/n) of pain over the previous 7 days, and (iii) *relief of symptoms* (collapsed to 3 categories: a little, moderate, or significant) using a 7-point Likert scale. Also, achieving 2 out of 3 of these measures was considered a clinical responder.

The 3-Month Follow-Up Assessment. At 3 months after detoxification, the research assistant contacted the patient, reviewed the medical record, and in some cases spoke with the patient’s physician to obtain information for the *Clinical Outcome* questionnaire. For pain and stool habit, the *Diary Card* was collected from the patient via mail.

NC Controlled Substances Patient Query (<https://nccrsph.hidinc.com/>). This database contains pharmaceutical dispensing records for all patients in the filling prescriptions in the state of North Carolina for the previous 2 years. Thus, if a patient went back on narcotics, we could identify the date it was prescribed and filled and compare this with the date of detoxification. The principal investigator (D.A.D.) accessed these records for all patients by the close of the study to determine which patients went back on narcotics and how many days after their detoxification their first prescription was filled. For subjects who did not reside within the state of North Carolina, contact was made with subject’s referring physicians to obtain similar data.

Data management and statistical methods

Descriptive statistics were calculated in the first aim for questionnaire items and scores for scales measured in order to

characterize the NBS patients before detoxification. Means and frequencies were calculated for all continuous variables, and frequencies were determined for all categorical variables.

The second aim looked at the process itself, and each subject’s response to treatment. Descriptive statistics were calculated regarding postdetoxification clinical, diary, and psychosocial outcome data. A difficulty score was calculated from process measures: whether the patient was prone to addictive behavior, the protocol was interrupted, how committed to the detoxification, response to withdrawal, the number of side effects rated moderate or higher, modified or negotiated withdrawal, and threatened to sign out against medical advice. Finally, response to detoxification was calculated, as described above.

For the third aim, baseline variables included a subset of those examined in the first aim, and bivariate associations between these variables and response status and each of the four component criteria for response were calculated and compared between yes/no groups: for continuous variables, means, and s.d. were calculated per category and compared by Wilcoxon Mann–Whitney tests, and for categorical variables, frequencies per category were determined and compared via χ^2 analyses with Fisher’s exact test.

For the fourth aim, response at 3-month follow-up was determined using data from 3-month follow-up questionnaires. The 3-month and overall recidivism rate (different follow-up periods per patient) were examined. Data from the NC Controlled Substances Patient Query provided information for all NC patients of whether they refilled narcotics and when. Data were also obtained for a few out-of-state patients. The proportion of those taking narcotics was calculated, as was the mean length of time (days) since detox before going back on narcotics and the mean length of time staying off narcotics for those who stayed off. As the length of follow-up time differed between individual patients, recidivism rates were calculated both at 3 months (as most everyone had a 3-month follow-up period) and then as much time as each follow-up allowed.

Change scores between pain and psychosocial measurements were compared from before to after detox by Wilcoxon signed rank tests. Pain (VAS Abdominal, VAS non-GI, General Well-being, McGill) and diary bowel movement scores were also compared across time (before detox, after detox, and 3-month follow-up by whether refilled narcotics or not) using Wilcoxon signed rank tests. Response status and component criteria were compared after detox and 3-month follow-up by whether refilled narcotics or not using McNemar’s tests. Pain scores were also compared by refill status at 3 months by Wilcoxon Mann–Whitney (continuous) and Fisher’s exact (categorical) tests.

RESULTS

Study population and clinical characteristics

We studied 34 inpatients seen by the GI consult service and 5 outpatients referred to the GI clinic. The population was primarily female (92.3%), white (87.2%), well educated (14.5 ± 2.3 years of school), and young to middle aged (39.9 ± 13.4 years). They reported pain symptoms for 15 ± 16.1 years, and were clinically

disabled with 82.1% being out of work because of their health. They went to physicians 15.3 ± 10.1 times in the previous 6 months, were hospitalized 6.5 ± 6.1 times in the past 2 years, and reported 6.4 ± 2.0 surgeries in their lifetime.

Table 1 reports pain and other clinical and psychosocial data obtained before detoxification. Notably, pain scores were very high, for example, the McGill Pain total scores (17.2 ± 10.2) for

NBS compares with 13 for women in labor and 11 for postoperative pain. Also, the diagnoses varied across several conditions including, postoperatively, inflammatory bowel disease (Crohn's disease more than ulcerative colitis), functional GI diagnoses (irritable bowel syndrome and functional abdominal pain), and other functional somatic syndromes (e.g., fibromyalgia). Contrary to expectations, these patients did not have constipated stools;

Table 1. Baseline pain, clinical, and psychosocial data

Pain parameters				
	All			
	N	Mean±s.d.		
Abdominal pain level today—VAS	39	52.9±28.8		
Non-GI pain level today—VAS	38	41.2±33.4		
	N	%		
Abdominal pain—Likert scale				
0: None/mild	9	23.08		
1: Moderate	14	35.9		
2: Severe/very severe	16	41.03		
	N	Mean±s.d.		
FBDSI	39	257.1±139.6		
	N	%		
FBDSI—categories				
Mild: <37	1	2.56		
Moderate: 37 to <110	7	17.95		
Severe: ≥110	31	79.49		
	N	Mean±s.d.		
McGill Sum score	38	17.2±10.2		
Stool Habit				
	N	Mean±s.d.		
Total bowel movements in the past 7 days	33	12.5±16.5		
	All			
	N	%	Mean	s.d.
BSS constipated stool	7	21.21	1.43	0.53
BSS normal stool	10	30.3	4	0.82
BSS diarrheal stool	16	48.48	6.5	0.52
Diagnosis				
	All			
	N	%		
1. Functional GI	8	21.05		
1: IBS	3	37.5		
2: Functional abdominal pain	2	25		
3: Functional chest pain	1	12.5		
5: Functional dyspepsia	1	12.5		
7: Functional GB/sphincter of oddi	1	12.5		

Table 1. Continued

2. Structural GI	14	36.84
1: GERD/NERD	1	6.67
3: Pancreatitis	1	6.67
4: Ulcerative colitis	4	26.67
5: Crohn's disease	9	60
3. Functional somatic/other medical disorder	5	13.16
1: Fibromyalgia	3	30
4: Reflex sympathetic dystrophy	1	10
5: Other medical diagnosis	6	60
4. Postoperative and injury	11	28.95
Psychosocial		
	All	
	N	Mean±s.d.
CSQ, Catastrophizing sum score (0–36 range)	39	19.9±8.6
SF-36 Physical (0–100 range)	39	28.3±7.7
SF-36 Mental (0–100 range)	39	34.3±11.0
HADS Anxiety (0–21 range)	39	9.0±3.6
	N	%
Clinical anxiety (Y/N)		
0: No	26	66.67
1: Yes	13	33.33
	N	Mean ± s.d.
HADS Depression (0–21 range)	39	8.6±3.3
	N	%
Clinical depression (Y/N)		
0: No	28	71.79
1: Yes	11	28.21
SCL-90: Mean Global Severity Index	39	1.2±0.7
	N	%
ABUSE, sexual or physical		
0: No	16	41.03
1: Yes	23	58.97
	N	Mean ± s.d.
MSI total items rated 3–4, before detox	39	17.8±9.2
	All	
	N	%
MSI symptoms: Top 10 symptoms most frequently endorsed as 3 or 4		
Nausea	28	71.79
Feeling tired during the day	26	66.67
Pain in the lower belly below belly button	26	66.67
Weakness	25	64.1
Pain in upper stomach above belly button	25	64.1
Feeling filled up after eating just a small amount	24	61.54

Table 1. Continued

Bad sleep	22	56.41
Feeling pressure in your tummy	22	56.41
Difficulty in falling asleep at night	20	51.28
Bloating	20	51.28
Narcotics and other medications used		
	All	
	N	%
Narcotics		
Oxycodone/Oxycontin/MS Contin	24	61.54
Fentanyl patch	9	23.08
Dilaudid (Hydromorphone)	8	20.51
Hydrocodone	4	10.26
Other (Buprenorphine, meperidine, methadone)	15	25.64
Antidepressants		
SNRI	16	53.33
SSRI	9	30
TCA	2	6.67
Other	3	10
Benzo diazepines	18	46.15
Atypical Antipsychotic	13	33.33
Laxative	12	30.77

BSS, Bristol stool form scale; CSQ, coping strategies questionnaire; FBDSI, functional bowel disorder severity index; GB, gallbladder; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; MSI, Medical Symptom Inventory; NERD, nonerosive reflux disease; SCL-90, Symptom Checklist-90; SF-36, Short Form-36; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VAS, visual analog scale.

however, this may be because of being treated, e.g., 31% were on laxatives. The psychosocial impairment included high catastrophizing scores, and poor quality of life with disability (e.g., SF-36 of 28.3 ± 7.7) was as bad as patients with tetraplegia (score = 30) or liver transplant (score = 32), compared with healthy subjects (score = 53). Abuse history was present in more than half, with rape reported in over 1/4 of the patients, and clinical anxiety and depression was present in ~1/3. Remarkably, these patients also endorsed on average 34 other symptoms, and 18 were rated as severe in intensity. Excluding the abdominal pain, the items most frequently endorsed in decreasing order were: nausea, fatigue, weakness, early satiety, sleep disturbance, and bloating (all endorsed by over 50%).

Patients took narcotics for 5 years (60.8 ± 70.2 months), and 75.3 ± 78.0 mg morphine equivalents per day. Oral morphine preparations were taken by more than half of the patients (e.g., oxycodone, MS Contin), followed by a fentanyl patch, and oral dilaudid or hydrocodone. Other medications frequently used included antidepressants in 77%, primarily serotonin–norepinephrine reuptake inhibitors (SNRIs), benzodiazepines in 46%, and atypical antipsychotics in 33.3%. This likely relates to prescribing patterns operative within our functional GI clinical program.

Narcotic bowel diagnosis

The five diagnostic criteria for NBS first published in our previous paper (1) were developed from clinical experience. To further evaluate these criteria, all patients admitted for detoxification were given the criteria items to determine the frequencies of endorsement as a form of validation, and also to correlate with physician clinical diagnosis. The first criterion was required, i.e., to be on narcotics, and hence in **Table 2** this is 100%. Then, the endorsements for the other four criteria ranged from 79.4 to 87.2%. Of these patients, 89.7% endorsed at least two of the four criteria, and also at least three of the four criteria, and 64.1% endorsed all criteria. In addition, the physician authors (D.A.D. and A.O.A.) knowledgeable about NBS rated 81.6% of the patients studied to have NBS based on the assessment of the clinical findings. Thus, we see a strong association between the patients admitted for detoxification, and the diagnostic criteria. We recommend that a diagnosis of NBS be based on having pain associated with narcotics and at least three of the other four criteria.

Detoxification and process of care

Detoxification method. All patients underwent narcotic detoxification along with other treatments for pain management and to

Table 2. NBS criteria and endorsement by respondents

	All	
	N	%
Chronic or frequently recurring GI pain that is treated with acute high dose or continual narcotics (required)	39	100
1. The pain worsens or incompletely resolves with continued or escalating dosages of narcotics	31	79.49
2. There is marked worsening of GI pain when the narcotic dose wanes and improvement when narcotics are reinstated (“Soar and Crash”).	34	87.18
3. There is a progression of the frequency, duration, and intensity of GI pain episodes.	34	87.18
4. The nature and intensity of the pain is not explained by a current or previous gastrointestinal diagnosis.	37	94.9
Endorsed all 4 criteria	26	64.1
Endorsed at least 3/4 criteria	35	89.7
Endorsed 2/4 criteria	35	89.7

GI, gastrointestinal; NBS, narcotic bowel syndrome.

prevent withdrawal. Recommended guidelines (see **Appendix**) were provided to the treating physicians and supervised by the physician authors (D.A.D., A.O.A., and J.Z.) and/or the GI consultation fellows on the consultation service. The study was not protocol driven; however, the guidelines suggested were for the most part adhered to with only 26% minor deviations.

Protocol summary. The patient’s usual dosage of narcotic calculated in intravenous (IV) morphine equivalents was given as a continuous drip of morphine or hydromorphone on the first day (mean 89.8±66.9 mg/day of morphine). This amount was then reduced by a fixed proportion (ranging from 15 to 33% each day) until completely off narcotics. The detoxification lasted for 7.3±2.8 days for inpatients and 39.4±21.4 days for outpatients. Patients were placed on an antidepressant before or upon admission for pain management and an oral or IV benzodiazepine to reduce anxiety. Oral clonidine (0.1–0.4 mg/day) was given after the narcotic dosage was reduced to about half to block withdrawal effects and titrated to maintain adequate blood pressure, and PEG solution was given to treat constipation if present. Our team psychologist (S.R.W.) saw 59.0% of the patients to provide encouragement and support. A total of 89.7% of patients were successfully detoxified off narcotics, and 4 patients (10.3%) were tapered off narcotics but were prescribed tramadol by the resident physicians upon discharge. Only one of the four refused to come off narcotics and signed out against medical advice.

Clinical observations during detoxification. To understand patient behaviors and physician–patient interactions during the detoxification, the clinicians (D.A.D. and A.O.A.) and research coordinators (C.E.D.W., M.H.B., and R.R.K.-K.) coded several

predefined process-related observations that might affect completing or responding positively to the detoxification: (i) Was the patient prone to addiction behavior? (Yes 20.5%, no 79.5%), (ii) Was the patient successfully detoxified? (64.1% Probably/Definitely yes, 23.1% probably/definitely no, 12.8 missing or unsure), (iii) What was the patient level of commitment to the program? (91.9% Fully committed or mixed feelings, 8.1% partially or fully reluctant/resistant), (iv) What was the patient’s response to withdrawal? (55.6% None or slight difficulties, 44.4% moderate or very difficult), (v) Did the patient request to modify or negotiate the withdrawal protocol after starting? (Yes 16.2%, no 83.8%), (vi) Did the patient experience side effects? (Yes 81.8%, no 18.2%), (vii) Did the patient sign out against medical advice? (No 97.4%, yes 2.6%). From these seven questions, we created a “NBS Difficulty Score” with each item coded as 1 and with a higher score indicating more difficulty. The mean score of 2.1±1 was then used in the predictive analysis (see below).

Clinical response after detoxification. We used several outcome measures to determine clinical response: Primary was a ≥30% reduction in VAS pain from before to after detoxification and this occurred in 51.4% of patients. We also looked at other outcomes including adequate relief of pain and discomfort that was reported by 63.6%, relief of symptoms was reported as significant (29.7%), moderate (27.0%), and a little (27.0%), no change in 5.7%, and worsening (a little, moderate, or significant) was reported by 10.8%. Finally, we also calculated a responder rate based on predetermined criteria (off narcotics and 2 out of 3 of: (i) a >30% reduction in VAS abdominal pain, (ii) adequate relief, and (iii) significant, moderate, or a little relief of symptoms and the responder rate was 59.5%.

Figure 1 shows the before and after detoxification scores for the pain measures. All reductions were indicating, at least by 30%, a statistically significant and clinically meaningful reduction in abdominal and nongastrointestinal pain for the VAS and the McGill Pain questionnaire, which is included as a concurrent measure for convergent validation.

With regard to bowel habit, there was no change in the number of bowel movement/week (from 12.4±16.2 to 11.4±12.2 bowel movement/week) but there was a shift in stool consistency using the BSFS to a less constipated stool. The pre- and post-detoxification values were: constipated (BSFS 1 and 2) 21.2 to 6.5%, normal (BSFS 3–5) 30.3 to 38.7%, and diarrheal (BSFS 6 and 7) 48.5 to 54.8%, respectively.

With regard to psychosocial scores, there was significant decrease (improvement) in the catastrophizing coping score (before: 19.9±8.6, after: 16.4±8.3, $P=0.025$). This is notable because the assessment period before and after detoxification was only a few days. No significant differences were observed between before and after detoxification for HADS anxiety and depression or for the SCL-90 overall psychological distress.

Side effects. A coding sheet of 10 common symptoms seen to occur with narcotic withdrawal was created, and patients were asked if they occurred or not. A total of 81.8% patients reported

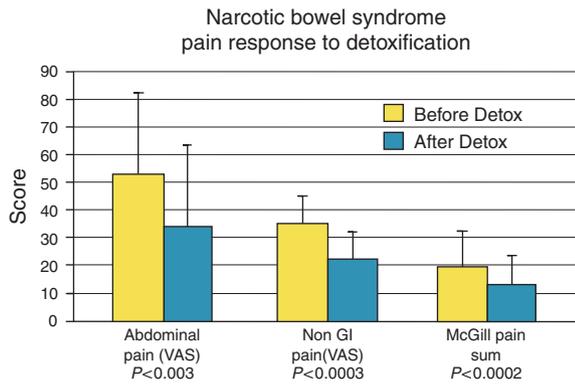


Figure 1. Pain response due to detoxification. The before and after detoxification levels of pain using a visual analog scale (VAS; 0–100) and the McGill Pain Questionnaire are shown. There is a statistically significant reduction in abdominal and non-gastrointestinal (non-GI)-related pain. This is also significant if one can define clinically meaningful response as >30% reduction (VAS abdominal pain 35%, VAS non-abdominal pain 42%, and McGill abdominal pain 31%).

on average 4.0 ± 3.1 symptoms, and 2.4 ± 2.5 of them were rated as moderate or severe. The most frequent symptoms were anxiety (51.3%), nausea, headache, and sleep difficulties (43.6% for each), abdominal pain as a side effect (38.5%), muscle aches and chills (33.3% for each), vomiting (23.1%), diarrhea (20.5%), and piloerection (15.4%). Patients were then asked to code the severity of each symptom as mild to severe (score 1 to 3). When present, the symptoms most severe were anxiety (2.32 ± 0.8), muscle aches (2.23 ± 0.8), chills (1.9 ± 0.7), nausea (1.9 ± 0.7), vomiting (1.9 ± 0.8), diarrhea (1.75 ± 0.9), and piloerection (1.33 ± 0.5). These findings, although possibly overlapping with the patient's presenting symptoms, seem consistent with some degree of narcotic withdrawal response.

Identification of factors associated with detoxification and clinical response

Analyses were conducted to determine which clinical and psychosocial variables are best associated with successful detoxification (i.e., completely tapering off narcotics), or being a responder: adequate relief, reduction in symptoms, and $\geq 30\%$ reduction in pain (2 out of 3), as well as the individual components. The independent variables included demographic factors, catastrophizing, HADS anxiety and depression, sexual abuse (rape), primary medical diagnosis, severity of symptoms (FBDSI), number of months on narcotics, number of days of detoxification, the narcotic bowel criteria, and the NBS difficulty score. We also included a validated measure of aberrant-related drug behavior of chronic pain patients when prescribed narcotics, the COMM (16).

Notably, a low COMM score (low addiction proneness) was associated with successful detoxification (detoxified: 0.82 ± 0.47 , not detoxified: 1.35 ± 0.53 , $P < 0.06$) and responder status (yes: 0.72 ± 0.42 , no: 1.19 ± 0.52 , $P < 0.02$; **Figure 2**). When looking at the individual outcome measures, adequate relief was associated with no predetoxification anxiety (yes: 20.8%, no: 61.5%, $P < 0.03$) and

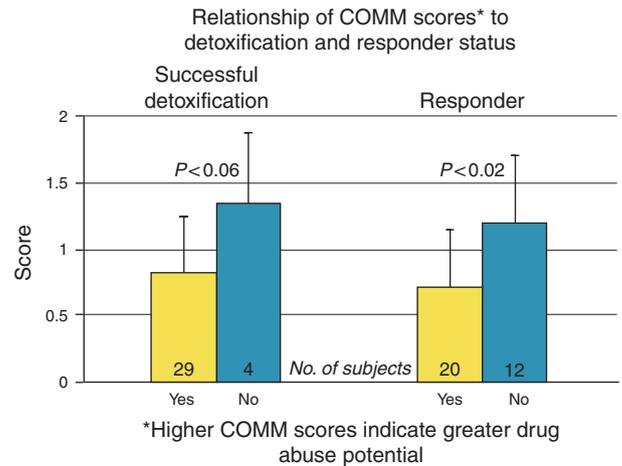


Figure 2. Relationship of Current Opioid Misuse Measure (COMM) scores to detoxification and responder status. It is noted that a low COMM score signifying lower abuse potential is associated with detoxification success and responder status. See text for details.

no history of sexual abuse (yes: 12.5%, no: 46.2%, $P < 0.05$), and adequate relief showed trend with the patient's perceived ability to decrease symptoms (yes: 2.67 ± 1.17 , no: 1.85 ± 1.14 , $P = 0.056$). Reduction in symptoms was associated with two NBS criteria: "GI pain worsened or incompletely resolved with continued narcotic use" (yes: 90.3%, no: 16.7%, $P < 0.003$) and "Chronic pain treated with high dose narcotics" (yes: 96.8%, no: 66.7% $P = 0.06$), the number of days of detoxification (yes 11.1 ± 12.0 , no 3.7 ± 21.2 , $P = 0.06$), and a high catastrophizing score (yes 21.1 ± 8.4 , no 13.7 ± 8.8 , $P = 0.076$). Finally, a $\geq 30\%$ reduction in pain was associated with the no predetoxification clinical depression (yes: 5.3%, no: 55.6%, $P < 0.002$) and positively associated with a perceived ability to decrease symptoms (yes: 2.8 ± 1.1 , no: 1.9 ± 1.2 , $P < 0.03$).

Clinical outcome at 3 months

The clinical outcome was obtained by determining when patients returned back to narcotics and also assessing the proportion remaining on narcotics at 3 months and comparing their pain scores.

Of the 39 patients studied, 2 patients were not analyzed as to whether they went back on narcotics because of unsuccessful detoxification or undetermined information, resulting in 37 patients. Of these 37 patients, 25 completed the 3-month assessment data.

Recidivism rates related to narcotic use. We were able to obtain accurate information for patients who resided in North Carolina by accessing the North Carolina Controlled Substances Reporting System (<https://nccsrsp.hidinc.com/>) that identifies controlled substances prescribed throughout the state for the previous 2 years. We obtained narcotic-use data on 36 patients based on the NC Controlled substance reporting system ($n = 30$), and also through medical records, and physician and patient reports ($n = 6$). Accurate time periods for recidivism were difficult to obtain as patients were treated over a 2-year study period, and hence patients seen earlier in the study were observed over

a longer period of time. Of the 36 patients, by the time of study completion, 24 patients (66.7%) restarted narcotic medication, and this occurred on average by 3 months (96.8 days±126.4), but the range was from 1 to 416 days. Of the 12 patients who stayed off narcotics with duration data, most were off for well over a year (493.5±371.1 days). As the follow-up period differed by subject, we displayed the recidivism in several ways. By 3 months, 48.7% went back on narcotics. However, seven subjects who were not on narcotics at 3 months subsequently went back on narcotics.

Figure 3 shows a survival probability graph for the 24 patients who went back on narcotics and the 12 who did not. Of note, 17% patients went back at 1 week, 50% at 3 months (93 days), 61% at 9 months, and 66.7% after 1 year (416 days).

The 3-month clinical assessment. At 3 months after detoxification, 21 of the 37 remaining patients (56.8%) remained off narcotics. Of these 37 patients, the follow-up data varied somewhat as to which patients had completed which questionnaires (62.2% (n=23) completed the 3-month NBS Assessment; 59.5% (n=22) completed the 3-month Diary Card) and also as to the number of

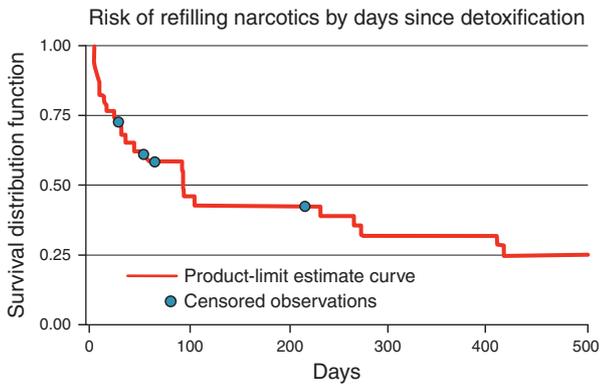


Figure 3. Survival graph for returning back on narcotics. A survival probability graph for the 24 patients who went back on narcotics and the 12 who did not is shown. Of note, almost 1/5 of this group (17%) went back at 1 week, 50% at 3 months (93 days), 61% at 9 months, and 66.7%, after 1 year (416 days).

days before refill or staying off narcotics (91.9%; n=34). Table 3 and Figure 4 report the clinical status for patients before and after detoxification and also at 3-month follow-up. Of note, for abdominal pain there continues to be a reduction in scores from before to after detoxification and to 3-month follow-up for patients who stay off narcotics. However, for those who go back on narcotics, the pain score reverts almost to predetoxification values. For non-GI pain (Table 3), there is a reduction in pain from before to after detox, but at 3 months there is no difference between those on narcotics and those not on narcotics, but the values are still lower than predetoxification.

DISCUSSION

The NBS is being increasingly recognized possibly because of better identification and/or a rise in its true prevalence resulting from increased opioid prescriptions for chronic nonmalignant pain (17,18). NBS is defined as the exacerbation of abdominal pain in the setting of continuous or escalating dosages of narcotics. NBS is often seen by gastroenterologists who are referred such patients with difficult to treat or refractory abdominal pain. How frequently patients given narcotics will get NBS is not known, but in one study of patients being seen for nonabdominal pain in a chronic pain clinic, this condition was diagnosed in 6.4% (4). There may be genetic or pharmacogenomic factors that lead a certain proportion of patients to develop this syndrome over others.

Since the publication of our case series and review 5 years ago (1), new evidence relating to pathophysiological mechanisms has emerged. Recent attention has focused on the CNS microglia: inflammatory cells that release cytokines that upregulate neural signals. Hutchinson *et al.* (19) described the concept of Toll-like receptor-mediated glial cell activation as central to neuropathic pain, impairment in opioid analgesia, and development of unwanted opioid side effects. Opioid agents are found in particular to possess Toll-like receptor-4 agonistic activity. Thus, narcotics act not only at classical opioid receptors to produce analgesia but also via Toll-like receptor-4 to activate glial cells to release cytokines and other pronociceptive agents, leading to a net reduction in

Table 3. Pain scores before and after detoxification and at 3-month follow-up

	Before detox		After detox		3-Month follow-up by whether refilled narcotics				3-Month refilled narcotics: yes vs. no	Change: Before detox change to off narcotics at 3 months (N)
	N	Mean±s.d.	N	Mean±s.d.	0: No		1: Yes			
					N	Mean±s.d.	N	Mean±s.d.	P value	P value
Abdominal pain (VAS)	39	52.9±28.8	37	34.3±28.4	13	15.6±23.1	10	43.9±20.8	0.0065	0.0566
Non-GI pain (VAS)	38	41.2±33.4	37	23.8±25.4	13	26.9±35.1	10	42.7±27.7	0.2404	1
General well-being	39	2.6±0.9	37	2.8±1.1	13	3.2±1.3	10	2.6±1.0	0.3179	0.6152
McGill summary score (0–45 range)	38	17.2±10.2	36	11.8±10.6	10	6.8±8.9	12	16.3±7.0	0.011	0.039

GI, gastrointestinal; VAS, visual analog scale. Bold values are statistically significant.

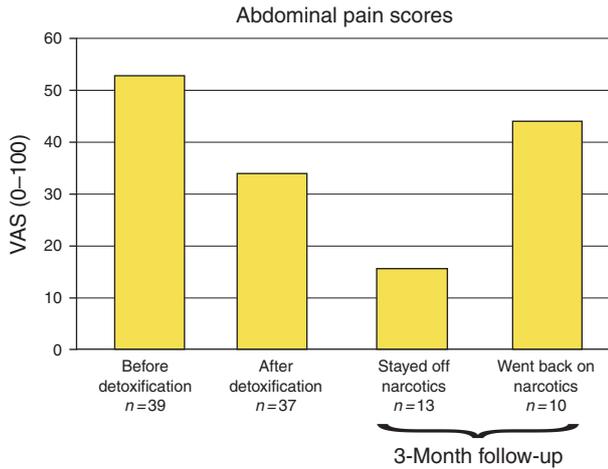


Figure 4. Visual analog scale (VAS) abdominal and non-gastrointestinal (non-GI) pain before and after detoxification and at 3 months. Abdominal pain reporting using a VAS before and after detoxification and at 3 months is shown. Notably, there continues to be a reduction in scores from before to after detoxification and at 3-month follow-up for patients who stay off narcotics. However, for those who go back on narcotics, the pain score reverts almost to predetoxification values.

analgesia and eventually hyperalgesia. More recently, Agostini *et al.* (20) developed an animal model for NBS using male Wistar rats that were treated daily with IV morphine and then evaluated pain response based on increased abdominal contractions to progressive rectal distension. NBS as shown by increased abdominal contractions developed after 1 week. The incipient pain response was attenuated by pretreating with minocycline, a glial cell inhibitor which supporting the concept of hyperalgesia because of glial cell activation. In addition, the delayed hyperalgesic effect, i.e., residual hyperalgesia after morphine treatment stopped, was inhibited by nor-binaltorphimine (nor-BNI), a κ -selective antagonist, and doxantrazole, a mast cell inhibitor. These and other studies may lead to future treatments that selectively produce opioid receptor analgesia without competing nociceptive effects or which can prevent the development of NBS.

We sought to understand the clinical features of these patients and the response to detoxification. We characterized this population as young- to middle-aged females, well educated, with a variety of structural and functional GI disorders or postoperatively. Pain was present for ~15 years, and narcotics were used for ~5 years. Despite being given 75 mg/day of IV morphine equivalent, the abdominal pain was rated as more severe than labor or postoperative pain and occurred with many other severe symptoms such as nausea, fatigue, bloating, and sleep disturbance. Approximately 1/3 of the patients had clinically significant anxiety or depression and had high catastrophizing scores. The degree of physical impairment was equivalent to or worse than tetraplegia or liver transplant, and over 80% were out of work because of health problems. The patients saw 15 physicians in 6 months and were hospitalized over 6 times in the previous 2 years, thereby suggesting high health-care costs. Undoubtedly, this is possibly one of the most severe groups of patients seen in GI practice.

We attempted to support the published diagnostic criteria for NBS (1) by identifying the frequency of items endorsed by patients who were admitted with this presumptive diagnosis. All patients fulfilled the main criterion pain associated with high dose or continual narcotics, and almost 90% endorsed three of the other four criteria. Also, 82% of the patients were diagnosed as NBS by the study investigators. We recommend that a diagnosis of NBS be strongly considered when patients with abdominal pain are on narcotics and fulfill three of the other four criteria.

We also evaluated the clinical response to detoxification treatment. Abdominal pain, the primary symptom of interest, was reduced significantly by all clinical parameters as was nonabdominal pain. Catastrophizing scores significantly improved. Notably, these patients did have a more normal stool pattern while on narcotics, and this may relate to concurrent use of laxatives or merely that constipation is not necessarily related to NBS. After detoxification, the stool frequency did not change, but there was a shift to a less constipated (i.e., softer) stool. Side effects occurred in over 80% of the patients, and reflected narcotic withdrawal including anxiety, nausea, headache, and sleep disturbance.

We also looked for clinical and psychosocial factors that might be associated with a clinical response and thus help clinicians identify who should undergo this treatment. Although several were identified, we thought most meaningful was that of a low score on the COMM, a measure of addiction proneness and emotional lability. This was associated with successful detoxification and clinical responder status. Finally, we assessed the clinical outcome and recidivism rate for patients successfully detoxified. As shown in **Table 3** and **Figure 4**, although the postdetoxification period showed improvement, the 3-month response particularly for abdominal pain related to whether or not patients had returned to narcotics. Hence, right after detoxification, the VAS abdominal pain scores dropped 35%, and at 3 months, those who remained off narcotics dropped 75% from predetoxification levels. However, for those who went back on narcotics, the pain scores went back up to 24% below predetoxification levels. Thus, the pain continues to improve while off narcotics.

As to the recidivism rate, by 3 months after detoxification, approximately half (48.7%) of the patients were back on narcotics. **Figure 3** indicates that ~1/4 will go back to narcotics within 1 week, half by ~3 months, and 3/4 by ~8 months. This leads to the question as to why would patients so quickly return to narcotics after detoxification if they have such a good pain response? We believe that patients who continue to take narcotics are doing so for reasons other than pain relief. Some report needing to be “numb” from life issues, or they value being “high.” Others acknowledge some desire to stay off narcotics but are unable to resist taking them again when prescribed by their physicians. Notably, patients with low COMM scores may be more likely to stay off narcotics, but this needs to be further studied.

There are some limitations to this study. Perhaps the most important limitation is that this is not a controlled study; however, having a control group who stayed on narcotics or received placebo for an extended period of time would be difficult to do and possibly unethical. In balance, the clinical response was remarkable

for patients who were doing poorly for so many years. Another possible difficulty is the “halo effect,” that is, the patients’ favorable responses may be influenced by the perceived status of our Functional GI clinical program. This may also bring in patients more motivated for treatment. Finally, there may be selection bias where patients more likely to respond are consciously or unconsciously recruited in to the study. Therefore, it is unclear if these results can be generalized to other clinical settings. Nevertheless, the very positive findings at least support the credibility of this method and future studies will help to identify the subset of patients who are more likely to respond.

Based on this evaluation, patients with narcotic bowel syndrome are characterized by having severe pain, multiple other symptoms, marked disability and unemployment, and high health-care use. Because of their impact on the health-care system, it is important to understand their clinical features and find ways to treat them. Currently, the best available treatment is detoxification, and this is associated with high clinical response rates with reduced pain scores that continue to improve at least 3 months after treatment. However, almost half the patients will return to using narcotics by 3 months.

ACKNOWLEDGMENTS

We acknowledge the assistance of the GI fellows from the UNC Division of Gastroenterology and the residents in the Department of Internal Medicine at UNC for making this study possible.

CONFLICT OF INTEREST

Guarantor of the article: Douglas A. Drossman, MD.

Specific author contributions: Douglas A. Drossman: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, administrative, technical or material support, and study supervision; Carolyn B. Morris: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis; Hollie Edwards: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision; Christina E.D. Wrennall: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision; Stephan R. Weinland: critical revision of the manuscript for important intellectual content; Ademola O. Aderoju: acquisition of data, analysis and interpretation of data, and administrative; Renuka R. Kulkami-Kelapure: Acquisition of data, analysis and interpretation of data, and administrative; Yuming J. Hu: statistical analysis and administrative; Christine Dalton: obtained funding and technical; Megan H. Bouma: acquisition of data and technical; Joseph Zimmerman: study concept and design and critical revision of the manuscript for important intellectual content; Ceciel Rooker: critical revision of the manuscript for important intellectual content; Jane Leserman: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis; Shrikant I. Bangdiwala: study concept and design and statistical analysis.

Financial support: This study was funded by research grants from Pfizer and Salix Pharmaceuticals.

Potential competing interests: Douglas A. Drossman: consultant for Salix; Carolyn B. Morris, Christina E.D. Wrennall, Stephan R. Weinland, Ademola O. Aderoju, Renuka R. Kulkami-Kelapure, Yuming J. Hu, Christine Dalton, Megan H. Bouma, Ceciel Rooker, Jane Leserman, and Shrikant I. Bangdiwala: none.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Opioids can have effects on the bowel that affect slowing of motility, producing constipation, vomiting due to secondary gastroparesis, and ileus.
- ✓ It has recently been found that a small percentage of individuals on high or chronic dosages of opiates can get a paradoxical hyperalgesia with abdominal pain (narcotic bowel syndrome (NBS)).
- ✓ The mechanisms for NBS are beginning to be understood in terms of glial cell activation.
- ✓ There is little evidence that continued use of high-dose narcotics can improve NBS and seem to exacerbate it.

WHAT IS NEW HERE

- ✓ NBS is not related to any particular medical diagnosis and is associated with very poor health status and high health-care utilization.
- ✓ Narcotic detoxification is associated with improvement in abdominal and nonabdominal pain.
- ✓ Approximately half of patients detoxified from narcotics in a medical setting are back on narcotics by 3 months after detoxification.
- ✓ Patients who remain off narcotics continue to improve their pain scores, whereas patients who return to narcotics have worsening abdominal pain.

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APPENDIX

Management of Patients with Narcotic Bowel Syndrome (1)

Ademola Aderoju, MD, Jacob Kurlander, MD, Christina Davis, Patrick Barrett, MD, Douglas A. Drossman, MD

Patients on chronic narcotics who have been diagnosed with narcotic bowel syndrome (NBS) benefit from the gradual but complete discontinuation of all narcotic medications. This can be accomplished successfully in the inpatient setting. However, the following points should be noted:

- (1) *Effective communication* with the patient is essential. The rationale/benefit of stopping the narcotics and the withdrawal program itself must be explained in detail prior to initiation of the detoxification protocol. This should include affirmation of the patient's pain and an explanation of the underlying pathophysiology of NBS (i.e. altered motility and/or visceral hypersensitivity).
- (2) The explanation should emphasize the substitution of *non-narcotic medications for pain management* (e.g. TCAs, SNRIs) and the treatment of withdrawal symptoms (e.g. with clonidine and benzodiazepines). The patient should be reassured that s/he will not be abandoned in pain.
- (3) A constant *plan for narcotic withdrawal* should be in place. The physician should be prepared for the patient who attempts to negotiate for additional narcotics above the protocol dose. This may require a thoughtful inquiry into possible exacerbating factors (e.g. withdrawal symptoms or anxiety). Verbal reassurance and adjustment of ancillary medications may be necessary. In the motivated patient, the program very often proceeds successfully to completion if issues are properly addressed.
- (4) *Ongoing dialogue* is important as the detoxification process progresses. The patient's willingness to undergo the program is central to success. It often helps to involve family members prior to initiating the protocol as this provides added support for the patient.
- (5) *Follow-up care* is essential. There is little benefit in instituting a narcotic withdrawal program unless there is continuity of care in the outpatient setting.
- (6) *The Functional GI and Motility Program is available to assist in the inpatient process as part of a research protocol.* If you and the patient are interested please contact Christina Davis (Christina_davis@med.unc.edu or 966-0142) before you begin the detoxification and she will see and screen the patient for eligibility. She will be able to track the patient's progress and notify you if there are any difficulties. In addition, the patient will receive compensation for participating in this observational study.

TREATMENT PROTOCOL

1. Pain Management

- (a) A TCA (e.g. desipramine, nortriptyline @25–150 mg/qhs) or SNRI (e.g. duloxetine 30–90 mg. qd) should be started for immediate and long-term pain control and to help manage psychological co-morbidities (21). This can be initiated at a low dose with dose escalation over the duration of the detoxification process and afterwards. If possible this should be started at least a week prior to the detoxification program (i.e., started before hospitalization) and continued after discharge indefinitely for pain management.
- (b) Mirtazepine (15–30 mg. qhs) can be considered instead of or in addition to a TCA or SNRI if nausea is a prominent feature.
- (c) Quetiapine (Seroquel; 25–100 mg.) (22) can be used as a single nighttime dose (25–100 mg qhs) for adjunct treatment of pain either concurrently in house or after several weeks as an outpatient if the antidepressant is not sufficient for pain management. This agent is also helpful to treat sleep disturbance and anxiety, as well as to augment the pain benefit (22;23), and can be continued after discharge.

2. Narcotic Withdrawal

(a) Total narcotic daily dose should be converted to morphine equivalents using an appropriate calculator (e.g. Globalrph or Eprocrates, see also **Table 1**, or UNC pharmacy website: <http://pharmacy.intranet.unchealthcare.org/opiatechart.pdf>).

Opiate Conversion Table (Table 1)

Drug	IV/IM dosing	PO dosing	Equivalent IV Morphine	Equivalent IV Hydromorphone
Morphine (MS Contin, Roxanol)	10 mg	30 mg	10 mg	1.5 mg
Codeine (Tylenol #3) ^a	120 mg	200 mg	10 mg	1.5 mg
Fentanyl	0.1 mg (100mCg)	—	10 mg	1.5 mg
Fentanyl Patch	25mCg/hr patch	—	10–22 mg ^b	1.5–3.4 mg ^b
Fentanyl Patch	50mCg/hr patch	—	23–37 mg ^b	3.5–5.6 mg ^b
Fentanyl Patch	75mCg/hr patch	—	38–52 mg ^b	5.7–7.9 mg ^b
Fentanyl Patch	100mCg/hr patch	—	53–67 mg ^b	8–10 mg ^b
Hydromorphone (Dilaudid)	1.5 mg	7.5 mg	10 mg	1.5 mg
Hydrocodone (Vicodin, Lortab, Norco)	—	30 mg	10 mg	1.5 mg
Levorphanol	2 mg	4 mg	10 mg	1.5 mg
Meperidine (Demerol)	75 mg	300 mg	10 mg	1.5 mg
Oxycodone (Percocet, Oxycontin)	—	20 mg	10 mg	1.5 mg
Oxymorphone (Opana)	1 mg	10 mg	10 mg	1.5 mg
Buprenorphine (Buprenex, Subutex)	0.4 mg	—	10 mg	1.5 mg
Butorphanol	2 mg	—	10 mg	1.5 mg
Nalbuphine (Nubain)	10 mg	—	10 mg	1.5 mg
Pentazocine (Talwin)	—	50 mg	10 mg	1.5 mg
Methadone ^c	5 mg	10 mg	10 mg	1.5 mg

^aUse caution in converting doses greater than 65 mg due to decreasing efficacy at high dose; suggest making a dosage reduction.

^bVariable absorption with transdermal fentanyl. Most conversion data available for transdermal patches underestimate patch strength. Therefore, converting from patch to iv morphine may give you a falsely elevated morphine dose. It is best to choose a number in the bottom 1/3 of the range.

^cMethadone has considerable interpatient variability and has a bi-phasic half-life. Please consult a clinic pharmacist for conversion and correlate with clinical analgesic response.

(b) This should be administered on day #1 of detoxification. In the inpatient setting, intravenous morphine (or hydromorphone in the case of a morphine allergy) as a continuous drip should be used. Be sure to remove the fentanyl patch if present. Special attention should be paid to the conversion of fentanyl patches. The equivalence varies by patch strength and conversion is not done by changing the transdermal dose to and iv fentanyl dose then to morphine. Rather, each patch has variable absorption and has a range of iv morphine equivalencies, please see **Table 1**. For outpatients, tapering can occur using oral medications, i.e., reduce by one dose (about 10–20%) each week.

(c) Giving the appropriate dose on day #1 is essential as a lower dose could lead to preliminary withdrawal symptoms, potentially sabotaging the process. THE NARCOTICS MUST BE ADMINISTERED CONTINUOUSLY, NOT PRN AND PREFERABLY NOT SCHEDULED. A PCA pump is used to minimize the likelihood of withdrawal symptoms.

(d) The narcotic dose should be weaned gradually, with a reduction of 10 to 33% of the dose given on day #1 every 24 hours. In general, slower tapers should be used for patients with more chronic and entrenched narcotic use. However, it is not the initial dose but the continuity of the dosing that avoids “soar crash or withdrawal effects.” The detoxification duration is between 4 and 11 days.

(e) Clonidine acts to block withdrawal effects and reduce diarrhea, anxiety and bowel-related pain. It should be initiated routinely when there is 50% reduction in narcotic dosage, or earlier to help control withdrawal symptoms (e.g., anxiety, diaphoresis, piloerection, diarrhea, muscle aches, shakiness).

(i) A reasonable starting dose is 0.1 mg po BID or TID.

(ii) Alternatively, this can be given as a patch that delivers the chosen daily dose (0.1, 0.2 or 0.3 mg and is replaced weekly).

(iii) The dose can be increased up to a total daily dose of 0.6 mg (usually 0.2–0.4 mg) for desired effect. The patient should be monitored closely for hypotension and orthostasis.

(iv) Clonidine can be rapidly tapered off or continued for several weeks, or indefinitely, depending on the patient’s perceived potential for relapse and the overall clinical benefit.

3. Constipation

- (a) Polyethylene glycol (PEG solution) can routinely be used for opioid-induced constipation, 1-3 glasses a day as needed.
- (b) If there is severe constipation and a KUB shows a large amount of stool, a complete flush (e.g., colonoscopy prep) should be instituted prior to daily dosing.
- (c) Methylnaltrexone (Relistor) given SQ 6 or 12 mg. q 2 days is an alternative treatment option if constipation is severe and not initially responsive to PEG solution.

4. Anxiety reduction

- (a) A benzodiazepine should be started on day #1 for anxiety. A reasonable option is lorazepam 1 mg po q 6 hrs and, if needed, IV is also permitted initially. This dose can be increased (e.g. for uncontrolled anxiety) or decreased (e.g. for unwanted sedation) as appropriate. The benzodiazepine should be discontinued at the end of the narcotic taper.

5. Psychological Treatment

- (a) Ideally we would like to have concurrent psychological care during the detox program. The benefit would be to provide supportive care and to institute pain management strategies.
- (b) Stephan Weinland PhD (Stephan_Weinland@med.unc.edu) can be available as a consultant and to work with the patient during the detox process on an as-needed and availability basis with the approval of the GI consult service.

The main obstacles to successful detoxification are:

- (1) Poor physician–patient communication, e.g. perceived lack of empathy, failure to validate pain, or poor explanation of rationale and benefits of detoxification.
- (2) An unmotivated patient (may need better education from physician).
- (3) Starting with too little narcotics on day #1 (make sure opioid-equivalence conversion is accurate).
- (4) Reducing the dosage too fast or going up and down in negotiation.
- (5) Administering the narcotics PRN instead of when scheduled (can precipitate withdrawal symptoms).
- (6) Failure to recognize and adequately address exacerbating factors, e.g. anxiety and withdrawal symptoms.

It is important to note that the *sine qua non* for successful detoxification is the physician's relationship with the patient, and the patient's acceptance of the detoxification plan.

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NARCOTIC BOWEL SYNDROME INPATIENT DETOXIFICATION CHECKLIST*Communication strategies for successful detox*

- Explain the rationale for the narcotic taper and provide realistic expectations (i.e., some pain may continue)
- Explain the underlying pathophysiology (e.g., altered motility, visceral hypersensitivity).
- Explain substituting alternative medications (TCAs, SNRIs) for narcotics + treating withdrawal side effects.
- Establish firm plan up front.
- Involve family members in the plan.
- Keep open an ongoing dialog.
- Affirm the patient's pain.

Preparation

- If severe constipation, obtain KUB. If large amount of stool, do a colonoscopy prep before narcotic taper.
- Start a TCA (e.g. desipramine, nortriptyline 25-150mg/qhs) or SNRI (e.g. duloxetine 30-90mg qd) ideally one week before detoxification for pain/psych comorbidity. Mirtazapine (15-30mg. qhs) may be used instead if nausea is prominent. May start low and escalate. Start at time of admission if not already done.

Narcotic taper

- Calculate total narcotic daily dose in morphine equivalents using a narcotic equivalence converter (<http://www.medcalc.com/narcotics.html>).
 - Total narcotic daily dose: _____ mg morphine equivalents
- On day #1 of detoxification, discontinue narcotics including any fentanyl patch. Then administer IV morphine at 100% of the daily narcotic dose. Give as a continuous drip, NOT as PRN or scheduled dosing. Hydromorphone may be used if there is morphine allergy.
- Every 24 hours, reduce the total narcotic dose by 10–33% of the dose given on day #1. Plan for 4 to 11 days of detoxification, with slower tapers reserved for patients with more chronic narcotic use.
 - Planned duration of taper: _____ days
 - Daily dose reduction = Total narcotic daily dose (mg)/taper duration (days) = _____ mg/day
- For withdrawal effects (diarrhea, anxiety, bowel-related pain, diaphoresis, piloerection, muscle aches, shakiness), give clonidine after 50% reduction in daily narcotic dose, or sooner. Start 0.1 mg po BID or TID or as a transdermal dose (0.1, 0.2 or 0.3 mg) once weekly. Titrate as needed up to 0.6 mg daily, staying alert to possible orthostasis or hypotension.
- For anticipated constipation, give polyethylene glycol 17g bid to tid as needed.
- For anxiety, give lorazepam 1 mg po q 6 hrs. May start IV instead. Titrate per anxiety and sedation.
- The GI and Motility Program can assist if the patient would like to enroll in an observation study. Contact: Christina_davis@med.unc.edu or 966-0142. If eligible, the patient gets compensation.

Possible problems

- Pain/anxiety/sleep disturbance: Increase TCA or SNRI. Can also add quetiapine 25–100mg qhs.
- When using clonidine be alert to orthostasis or hypotension.
- Severe constipation: Give methylnaltrexone (Relistor) 6–12 mg SC q 2 days if resistant to PEG.
- Attempts to renegotiate taper: Give verbal reassurance and adjust ancillary medications, not narcotics.
- For additional supportive care and pain management: Stephan Weinland, PhD, can consult with the patient during the detox process with the approval of the GI consult team. (Stephan_Weinland@med.unc.edu)

Discharge – Arrange follow up care

- Continue TCA, SNRI, and/or quetiapine.
- Clonidine can be rapidly tapered off or continued for several weeks, or indefinitely, depending on the patient's perceived potential for relapse and the overall clinical benefit.
- Discontinue benzodiazepines.