AP&T Alimentary Pharmacology and Therapeutics

Development and validation of a clinical prediction score (the SCOPE score) to predict sedation outcomes in patients undergoing endoscopic procedures

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Publication data
Submitted 19 March 2014
First decision 4 April 2014
Resubmitted 16 April 2014
Accepted 17 April 2014
EV Pub Online 11 May 2014

This article was accepted for publication after full peer-review.

SUMMARY

Background
Use of anaesthesia services during endoscopy has increased, increasing cost of endoscopy.

Aim
To identify risk factors for and develop a clinical prediction score to predict difficult conscious sedation.

Methods
We performed a retrospective cross-sectional study of all patients who underwent oesophagogastroduodenoscopy (OGD) and colonoscopy with endoscopist-administered conscious sedation. The endpoint of difficult sedation was a composite of receipt of high doses (top quintile) of benzodiazepines and opioids, or the documentation of agitation or discomfort. Univariate and multivariate analyses were performed to measure association of the outcome with: age, sex, body mass index (BMI), procedure indication, tobacco use, self-reported psychiatric history, chronic use of benzodiazepines, opioids or other psychoactive medications, admission status and participation of a trainee. A clinical prediction score was constructed using statistically significant variables.

Results
We identified 13 711 OGDs and 21 763 colonoscopies, 1704 (12.4%) and 2299 (10.6%) of which met the primary endpoint, respectively. On multivariate analysis, factors associated with difficulty during OGD were younger age, procedure indication, male sex, presence of a trainee, psychiatric history and benzodiazepine and opioid use. Factors associated with difficulty during colonoscopy were younger age, female sex, BMI <25, procedure indication, tobacco, benzodiazepine, opioid and other psychoactive medication use. A clinical prediction score was developed and validated that may be used to risk-stratify patients undergoing OGD and colonoscopy across five risk classes.

Conclusions
Using the Stratifying Clinical Outcomes Prior to Endoscopy (SCOPE) score, patients may be risk stratified for difficult sedation/high sedation requirement during OGD and colonoscopy.

Aliment Pharmacol Ther 2014; **40:** 72–82

doi:10.1111/apt.12786

INTRODUCTION

Sedation is an integral aspect of endoscopic examination in the US, where it is used to reduce anxiety, minimise discomfort and maximise patient safety.[1] Adequate sedation has been found to increase patient satisfaction and result in greater willingness to undergo repeat procedures. Conversely, inadequate sedation results in patient discomfort, higher rates of incomplete examinations and less patient willingness to undergo a repeat procedure.[2]

In the past, most diagnostic endoscopic procedures have been performed under moderate sedation,[1] but in the past decade the use of monitored anaesthesia care, generally coupled with deep sedation with propofol, has increased significantly, from 11% in 2000 to 23.4% in 2006 in a Medicare cohort,[3] and from 13.6% in 2003 to 35.5% in 2009 in a commercially insured cohort.[4] By one estimate, anaesthesia services could be involved in over 50% of endoscopic procedures by 2015.[5] This increased utilization has also been associated with an increase in cost, with anaesthesiologist supported procedures costing 20–50% more than those with endoscopist-administered sedation.[3, 4] Given these developments, efforts are warranted to risk-stratify patients who may be more or less difficult to sedate with conscious sedation.

There are several reasons endoscopists may prefer deep sedation and the use of anaesthesia services to conscious sedation. Deep sedation may potentially result in decreased patient responsiveness and movement during the procedure, allowing shorter procedure times as compared to conscious sedation.[6] Some have also speculated that deeper sedation may allow for more complete examinations, especially in the case of colon cancer screening; however, three studies have suggested that polyp detection rate is not affected by level of sedation.[7–9] In addition, one recent study has shown that the use of anaesthesia services during colonoscopy is associated with a modest increase in complications such as aspiration pneumonia.[10]

The aim of the present study was to identify those who are at risk of being difficult to sedate or having a high sedation requirement, and to develop a clinical prediction score that can be used by practitioners to risk-stratify patients.

METHODS

Database, patients and procedures

Subject data was extracted from the electronic endoscopy record system (ProVation, Wolters Kluwer Health, Philadelphia, PA, USA) at Columbia University Medical Center, which was fully implemented in September 2006. The database was initially queried for the 6.5-year period between the dates of 1 October 2006 and 31 March 2013 for patients undergoing oesophagogastroduodenoscopy (OGD) or colonoscopy. If a patient had more than one of each type of exam performed during the time period, only the first was included in the analysis. Patients in which multiple procedure types were done sequentially or on the same day were excluded. Procedures that were performed utilizing anaesthesia services for sedation were also excluded, as were procedures in which diphenhydramine was administered, since the additional sedative effect of diphenhydramine precluded our ability to determine whether this was given prophylactically or in response to high sedation requirements.

Nursing staff in the endoscopy unit routinely perform a pre-procedure patient interview, and solicit information including patient height, weight, history of tobacco use, history of psychiatric illness and medication use. Data ascertained from this interview and other demographical data were collected from the electronic endoscopy record system on patient age, gender, height, weight, tobacco use, alcohol use, psychiatric history, home medication use, admission status and presence of a gastroenterology trainee (fellow) during the procedure.

Among the patient characteristics studied, not all were consistently reported in the database; of the procedures included in the study, information on tobacco use was available in 85.8% of cases, psychiatric history in 84.7%, medication use in 94.0%, admission status in 98.9% and American Society of Anaesthesiologists (ASA) class in 89.8%. BMI could be calculated from height and weight in 84.0% of cases. Alcohol use was reported in 85.7% of cases; however, using the data available, we were unable to differentiate between occasional, moderate and heavy alcohol use, so alcohol use was not included in the study as a covariate. All other variables were present in all procedures studied.

Study variables

Patient home medication use was obtained from the endoscopy database, and patients were classified as taking opioids, benzodiazepines and other psychoactive medications (anti-depressants and anti-psychotics). This was done by searching each patient's medication list for a series of generic and brand names of the above classes of medications (See Table S1).

Body mass index (BMI) was calculated from self-reported height and weight according to the formula BMI = weight/height.[2] BMI was divided into six groups

for statistical analysis due to the potentially nonlinear effect of this variable on the outcome.

Psychiatric history (i.e. a diagnosis of depression, anxiety disorders, or other psychiatric diagnoses) is assessed as part of the routine pre-endoscopy interview performed by nursing staff. Divulgence of psychiatric history was voluntary on the part of the patient, and although specific psychiatric diagnoses were also collected as part of the interview, the low rate of completion of this latter specific field in the database necessitated psychiatric history being studied as a binary variable.

Because some procedures had more than one indication listed, and the study design necessitated a single indication for each procedure, the indication for the purposes of the study was assigned hierarchically. For OGD, in the order of priority for indication was acute gastrointestinal (GI) bleeding, abdominal pain, reflux/oesophagitis/Barrett's surveillance and then other. For colonoscopy, in the order of priority was acute GI bleeding, diagnostic/other (including abdominal pain and nonacute bleeding), surveillance and then screening.

Study endpoints

Patients received intravenous fentanyl, meperidine and midazolam in various combinations. The quantity, type and frequency of sedative administration were at the discretion of the endoscopist. A nurse administered the medications upon the instruction by the endoscopist. For this study, opioid requirement was measured in units of fentanyl equivalents. Conversion of meperidine dose to fentanyl dose was done with the following formula:[11] fentanyl dose = meperidine dose * (4/3000).

The primary endpoint of this study was difficult sedation/high sedation requirement, which was a composite of receipt of high doses (top quintile) of both benzodiazepines and opioids, or the documentation of agitation, discomfort, or other difficulty with sedation in the endoscopist's note. In the ProVation software, endoscopists have the option of selecting from one of several phrases regarding difficult sedation or inserting their own free-text entry. Notes were analysed for presence of these phrases and other common keywords related to difficult sedation; if any of these words or phrases were found, the procedure was classified as difficult.

As a secondary endpoint (i.e. sensitivity analysis), we repeated the derivation of risk factors, now restricting the outcome to those procedures in which the endoscopist documented agitation, discomfort, or other difficulty with sedation as above.

Due to the potential for variability in dosing of sedative medications between providers, we performed additional analysis of sedative medication dosing of individual providers. Of the 64 individual providers who had performed endoscopic procedures during the study period, 41 had performed greater than 100 procedures total during the period and were included in this analysis. For providers who had performed greater than 25 of each procedure type, the cut-off for the top quintile of midazolam and fentanyl-equivalent doses were calculated. Using the endpoint of top quintile doses of both midazolam and fentanyl equivalents, now calculated per individual provider, an additional multivariate logistic regression was performed as a sensitivity analysis.

Statistical analyses and clinical prediction score development

Univariate comparison of patient characteristics was performed through use of chi-square tests, with the addition of Cochran-Armitage trend tests for ordinal variables. Multivariate logistic regression models with both the primary endpoint of difficulty with sedation/high sedation requirement and sensitivity analysis with difficult sedation were performed. Covariates in these models included age, gender, BMI, procedure indication, tobacco use, psychiatric history, home benzodiazepine, opioid, and other psychoactive medication use, admission status and presence of a GI trainee.

Variables that were found to meet statistical significance in logistic regression with the primary endpoint were retained and used to develop clinical prediction scores following the method outlined by Sullivan, *et al.*[12] Beta-coefficients from the logistic regression model were scaled and rounded to develop a point system for each procedure type. In the prediction score, patients with age >70 years were excluded, as the risk of difficult sedation/high sedation requirement in this group was very low (3.6% for OGD, 5.1% for colonoscopy). Five risk classes for difficult sedation/high sedation requirement were constructed to maximise utility, and the prevalence of the primary endpoint was found in the original cohort for each risk class.

Validation of the clinical prediction scores

After development of the clinical prediction scoring system, the endoscopy database was queried for OGDs and colonoscopies performed during a subsequent time period: 1 April 2013 to 30 September 2013. These additional data were used to validate the clinical

prediction scores by similarly calculating the prevalence of difficult sedation/high sedation requirement in each risk class. Test characteristics for each procedure type and risk class were compared between the derivation and validation cohorts using chi-square and Fisher exact tests.

All analyses were performed using SAS version 9.4 (Cary, NC, USA). The Institutional Review Board at Columbia University Medical Center approved this study in February 2013.

RESULTS

A total of 28 539 OGDs and 34 713 colonoscopies were performed during the 6.5-year period spanning 1 October 2006 to 31 March 2013. After excluding patients who had OGD and colonoscopy on the same day (n = 4672, 7.4%), had an anaesthesiologist assist in the procedure (n = 7875, 12.5%), or received diphenhydramine during the procedure (n = 2995, 4.7%), and excluding all but the first chronological exam of each type per patient, a total of 13 711 OGDs and 21 763 colonoscopies were included in analysis (Table 1). Patients who had an anaesthesiologist assist in the procedure were 47.8% male, and had a mean age of 59.2, similar to those who did not (43.6% male, mean age 59.0). Among those who had an anaesthesiologist assist in the procedure, 7.0, 79.4, 12.5 and 1.2% were ASA class I–IV respectively, while among those who had endoscopist-administered sedation, 25.8, 64.6, 9.1 and 0.5% were ASA class I–IV respectively.

OGD analysis

In the OGD group, we identified 137 (1.0%) procedures in which the endoscopist noted difficulty with sedation as defined by agitation, discomfort, or other behaviours impacting the procedure. The 80th percentile of midazolam and fentanyl-equivalent doses was 5 mg and 125 μg, respectively. The number of patients who fell above the 80th percentile for both medications and were considered to have high sedation requirement was 1596 (11.6%). Of those who met criteria for difficulty with sedation as documented by the endoscopist (n = 137), 29 (21.2%) had high sedation requirement, while among those who did not meet criteria for difficulty with sedation (n = 13 574), 1567 (11.5%) had a high sedation requirement (P = 0.0005). The mean midazolam and fentanyl-equivalent doses in those who met criteria for difficulty with sedation were 3.43 mg and 83.0 μg respectively, while the mean doses were 3.09 mg and 79.2 μg among those who did

Table 1 | Characteristics of patients included in analyses

Characteristic – no. (%) unless noted	OGD (n = 13 711)	Colonoscopy (n = 21 763)
Age (mean ± s.d.)	57.4 ± 17.4	60.8 ± 12.7
18–29	1084 (7.9)	437 (2.0)
30–39	1411 (10.3)	681 (3.1)
40–49	1857 (13.5)	1969 (9.1)
50–59	2576 (18.8)	6859 (31.5)
60–69	3073 (22.4)	6174 (28.4)
70+	3710 (27.1)	5643 (25.9)
Male sex	5971 (43.6)	9577 (44.0)
BMI – kg/m^2		
Mean ± s.d.	26.75 ± 6.42	26.86 ± 5.26
Median (range)	25.55 (11.11–83.17)	26.13 (12.15–62.19)
Indication		
OGD – acute GI bleed	2105 (13.4)	
OGD – abdominal pain	4258 (31.1)	
OGD – reflux, oesophagitis, Barrett's	3082 (22.5)	
OGD – other	4266 (31.1)	
Colon – acute GI bleed		882 (4.1)
Colon – diagnostic/other		6428 (29.5)
Colon – surveillance		4175 (19.2)
Colon – screening		10 278 (47.2)
Current or prior tobacco use	1140 (11.3)	2289 (11.3)
Self-reported psychiatric history	1340 (13.4)	2231 (11.1)
Home medication use		
Benzodiazepines	683 (5.6)	900 (4.3)
Opioids	330 (2.7)	426 (2.0)
Other psychoactive medications	1676 (13.7)	2799 (13.2)
In-patient	3625 (26.7)	1359 (6.3)
Presence of GI fellow during procedure	4805 (35.0)	3222 (14.8)
High sedative dose requirement	1596 (11.6)	1974 (9.1)
ASA class		
Class I	3362 (26.4)	6593 (34.0)
Class II	7666 (60.2)	11 752 (60.6)
Class III	1624 (12.7)	1022 (5.3)
Class IV	17 (0.1)	3 (0.0)
Class V	74 (0.6)	18 (0.1)
Difficulty with sedation	137 (1.0)	446 (2.1)
High-dose requirement or difficulty with sed	1704 (12.4)	2299 (10.6)
Aborted (reason)	68 (0.5)	224 (1.0)
Poor bowel preparation quality	5 (7.4)	107 (47.8)
Difficulty with sedation	31 (45.6)	11 (4.9)
Cardiovascular or respiratory instability	10 (14.7)	5 (2.2)
Other or not documented	22 (32.4)	101 (45.1)

Table 2 | Univariate (chi-square) analysis using the primary composite outcome of difficult sedation mentioned in the procedure note and high sedation requirement defined by being in the top quintile of both benzodiazepine and opioid doses

	OGD		Colonoscopy	
Characteristic	Difficult and/or high medication requirement (n = 1704) (12.4%)	P value	Difficult and/or high medication requirement (n = 2299) (10.6%)	P value
Age				
18–29	288 (26.6)	**$P < 0.0001$**	119 (27.2)	**$P < 0.0001$**
30–39	338 (24.0)		185 (27.2)	
40–49	377 (20.3)		348 (17.7)	
50–59	316 (12.3)		778 (11.3)	
60–69	251 (8.2)		582 (9.4)	
70+	134 (3.6)		287 (5.1)	
Sex				
Male	735 (12.3)	$P = 0.712$	795 (8.3)	**$P < 0.0001$**
Female	969 (12.5)		1504 (12.3)	
BMI – kg/m^2				
<18.5	50 (15.4)	**$P = 0.005$**	51 (14.0)	**$P < 0.0001$**
18.5–25	595 (14.5)		948 (12.4)	
25–30	407 (13.2)		684 (9.1)	
30–35	180 (13.8)		315 (10.2)	
35–40	81 (17.2)		106 (10.6)	
40+	86 (19.4)		51 (11.2)	
Indication				
OGD – acute GI bleed	146 (6.9)	**$P < 0.0001$**		
OGD – abdominal pain	554 (13.0)			
OGD – reflux, oesophagitis, Barrett's	468 (15.2)			
OGD – other	536 (12.6)			
Colon – acute GI bleed			65 (7.4)	**$P < 0.0001$**
Colon – diagnostic/other			900 (14.0)	
Colon – surveillance			367 (8.8)	
Colon – screening			967 (9.4)	
Tobacco use				
Current or prior	174 (15.3)	$P = 0.291$	284 (12.4)	**$P = 0.007$**
Never	1265 (14.1)		1904 (10.6)	
Self-reported psychiatric history				
Yes	235 (17.5)	**$P = 0.0002$**	297 (13.3)	**$P < 0.0001$**
No	1184 (13.7)		1864 (10.5)	
Home medications				
Benzodiazepine use	121 (17.7)	**$P = 0.0009$**	181 (20.1)	**$P < 0.0001$**
Opioid use	60 (18.2)	**$P = 0.012$**	76 (17.8)	**$P < 0.0001$**
Other psychoactive medication use	256 (15.3)	**$P = 0.022$**	384 (13.7)	**$P < 0.0001$**
Admission status				
In-patient	292 (8.0)	**$P < 0.0001$**	113 (8.3)	**$P = 0.005$**
Out-patient	1388 (14.0)		2161 (10.7)	
Presence of GI fellow during procedure				
Fellow present	514 (10.7)	**$P < 0.0001$**	331 (10.3)	$P = 0.561$
Fellow not present	1190 (13.4)		1968 (10.6)	

Bold value indicates significance ($P < 0.05$).

Table 3 | Multiple logistic regression analysis using the primary composite outcome of difficult sedation mentioned in endoscopist notes and high sedation requirement defined by being in the top quintile of both benzodiazepine and opioid doses

	OGD			Colonoscopy		
Characteristic	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age			**P < 0.0001**			**P < 0.0001**
18–29	1	Ref		1	Ref	
30–39	0.84	0.70–1.01	P = 0.068	1.02	0.78–1.34	P = 0.874
40–49	0.65	0.54–0.78	**P < 0.0001**	0.60	0.47–0.76	**P < 0.0001**
50–59	0.34	0.29–0.41	**P < 0.0001**	0.38	0.30–0.48	**P < 0.0001**
60–69	0.22	0.18–0.26	**P < 0.0001**	0.30	0.24–0.38	**P < 0.0001**
70+	0.10	0.08–0.12	**P < 0.0001**	0.15	0.12–0.19	**P < 0.0001**
Sex						
Male	1	Ref		1	Ref	
Female	0.87	0.78–0.98	**P = 0.018**	1.50	1.37–1.65	**P < 0.0001**
BMI – kg/m2			P = 0.812			**P = 0.002**
<18.5	1.04	0.75–1.44	P = 0.817	0.94	0.68–1.29	P = 0.693
18.5–25	1	Ref		1	Ref	
25–30	1.03	0.89–1.19	P = 0.705	0.79	0.71–0.88	**P < 0.0001**
30–35	1.00	0.83–1.21	P = 0.984	0.84	0.73–0.97	**P = 0.014**
35–40	1.20	0.92–1.56	P = 0.177	0.79	0.64–0.99	**P = 0.037**
40+	1.02	0.79–1.33	P = 0.871	0.82	0.60–1.11	P = 0.202
Indication			**P = 0.0007**			**P < 0.0001**
OGD – acute GI bleed	1.18	0.90–1.54	P = 0.245			
OGD – abdominal pain	1	Ref				
OGD – reflux, oesophagitis, Barrett's	1.34	1.16–1.54	**P < 0.0001**			
OGD – other	1.18	1.03–1.35	**P = 0.018**			
Colon – acute GI bleed				1.19	0.79–1.80	P = 0.403
Colon – diagnostic/other				1.30	1.16–1.44	**P < 0.0001**
Colon – surveillance				1.12	0.98–1.27	P = 0.100
Colon – screening				1	Ref	
Current or prior tobacco use (vs. never)	1.04	0.87–1.24	P = 0.694	1.20	1.04–1.37	**P = 0.011**
Self-reported psych hx (vs. no psych hx)	1.23	1.01–1.49	**P = 0.044**	0.86	0.73–1.02	P = 0.092
Home medications (vs. nonuse)						
Benzodiazepine use	1.39	1.10–1.75	**P = 0.005**	2.09	1.73–2.52	**P < 0.0001**
Opioid use	1.41	1.04–1.92	**P = 0.028**	1.56	1.20–2.03	**P = 0.001**
Other psychoactive medication use	0.98	0.82–1.18	P = 0.860	1.21	1.04–1.40	**P = 0.013**
In-patient admission status (vs. out-patient)	0.99	0.71–1.39	P = 0.973	0.89	0.58–1.36	P = 0.581
GI Fellow present during procedure (vs. not present)	1.43	1.23–1.65	**P < 0.0001**	1.12	0.97–1.29	P = 0.122

Bold value indicates significance ($P < 0.05$).

not meet criteria ($P = 0.03$ for midazolam dose, $P = 0.34$ for fentanyl-equivalent dose). The combined primary endpoint of difficult sedation/high sedation requirement was found in 1704 procedures (12.4%). The top quintile of sedative medication dosing varied between individual providers for Midazolam (range 3.5–7 mg) and fentanyl equivalents (range 75–183 μg).

Univariate (Table 2) and multivariate (Table 3) analyses were performed using the primary endpoint, and the multivariate model was rerun for a sensitivity analysis, now restricted to the endpoint of difficulty with sedation as noted in the endoscopist's note (See Table S2). An additional multivariate model was performed using the endpoint of top quintile of sedative medication doses per individual provider (See Table S3). On multivariate analysis, age, male sex, indication, self-reported psychiatric history, benzodiazepine use, opioid use and presence of a GI trainee were found to be associated with the primary endpoint. On multivariate analysis using the secondary endpoint, female sex and tobacco use were additionally found to be associated with the endpoint, while male sex, indication, benzodiazepine use, opioid use and psychiatric history were not.

Colonoscopy analysis

In the colonoscopy group, we identified 446 (2.1%) procedures in which the endoscopist noted difficulty with sedation as defined by agitation, discomfort, or other behaviours impacting the procedure. The 80th percentile of midazolam and fentanyl-equivalent doses was 5 mg and 133.3 μg, respectively. The number of patients who fell above the 80th percentile for both medications and were considered to have high sedation requirement was 1974 (9.1%). Of those who met criteria for difficulty with sedation as documented by the endoscopist (n = 446), 121 (27.1%) had high sedation requirement, while among those who did not meet criteria for difficulty with sedation (n = 21 317), 1853 (8.7%) had a high sedation requirement ($P < 0.0001$). The mean midazolam and fentanyl-equivalent doses in those who met criteria for difficulty with sedation were 4.44 mg and 118.3 μg respectively, while the mean doses were 3.43 mg and 96.5 μg among those who did not meet criteria ($P < 0.0001$ for midazolam and fentanyl-equivalent doses). The combined primary endpoint of difficult sedation/high sedation requirement was found in 2299 procedures (10.6%). The top quintile of sedative medication dosing varied between individual providers for Midazolam (range 3.5–7 mg) and fentanyl equivalents (range 75–175 μg).

Univariate (Table 2) and multivariate (Table 3) analyses were performed using the primary endpoint, and the multivariate model was rerun for a sensitivity analysis, now restricted to the endpoint of difficulty with sedation as noted in the endoscopist's note (See Table S2). An additional multivariate model was performed using the endpoint of top quintile of sedative medication doses per individual provider (See Table S3). On multivariate analysis, age, female sex, BMI <25, diagnostic indication, tobacco use, benzodiazepine use, opioid use and other psychoactive medication use were associated with the primary endpoint. On multivariate analysis with the secondary endpoint, no additional variables were associated with the endpoint, however benzodiazepine use was found not to be associated with the endpoint.

Clinical prediction score

A scoring system, the Stratifying Clinical Outcomes Prior to Endoscopy (SCOPE) score, was developed based on factors significantly associated with the primary endpoint (Table 4). The most significant risk factors for both procedure types were younger age, followed by benzodiazepine and opioid use. For OGD, indication is a moderate risk factor, while male sex, psychiatric history and presence of a fellow are weak risk factors. For colonoscopy, indication, female sex and BMI were moderate risk factors, while tobacco use and other psychoactive medication use are weak risk factors.

Table 4 | The Stratifying Clinical Outcomes Prior to Endoscopy (SCOPE) scoring system, which can be used to risk-stratify patients for difficult sedation/high sedation requirement during OGD and colonoscopy

Characteristic	Number of points
OGD	
Age 18–29	10
Age 30–39	9
Age 40–49	7
Age 50–59	3
Age 60–69	0
Indication for reflux*	2
Indication for other category (not for reflux* or abdominal pain)	1
Male sex	1
Psychiatric history	1
Benzodiazepine use	2
Opioid use	2
Fellow present	1
Colonoscopy	
Age 18–29	10
Age 30–39	10
Age 40–49	6
Age 50–59	2
Age 60–69	0
Diagnostic indication	3
Female sex	3
BMI <25	2
Tobacco use	1
Benzodiazepine use	6
Opioid use	4
Other psychoactive medication use	1

* Reflux indication includes gastrointestinal reflux disease, oesophagitis and Barrett's oesophagus.

Five risk classes (SCOPE classes) were constructed for each prediction score, constructed with the number of point totals in each SCOPE class being divided approximately equally and to maximise utility of the score (Table 5). Rates of the primary endpoint in the derivation cohort and the validation cohort were calculated for each class. No statistically significant differences were seen between the rates of the primary endpoint in the derivation and validation cohorts. The area under the ROC curve for the models used to generate the OGD and colonoscopy clinical predictions scores were 0.679 and 0.648 respectively, indicating moderate association of the overall model with the outcome.

Table 5 | The comparison of SCOPE-class-specific difficult sedation/high sedation requirement rates in the cohorts used to derive and validate the clinical prediction scoring system. The per cent meeting the primary outcome in the derivation cohort can be used to estimate a patient's risk of difficult sedation/high sedation requirement based on their SCOPE score

	Derivation cohort		Validation cohort	
SCOPE class (no. of points)	Number of patients (%)	Primary outcome met (%)*	Number of patients (%)	Primary outcome met (%)*
OGD				
I (0–4)	3961 (39.6)	337 (8.5)	278 (44.8)	26 (9.4)
II (5–7)	1719 (17.2)	233 (13.6)	129 (20.8)	26 (20.2)
III (8–10)	2340 (23.4)	482 (20.6)	128 (20.7)	33 (25.8)
IV (11–13)	1903 (25.8)	491 (25.8)	82 (13.2)	25 (30.4)
V (14+)	78 (0.8)	27 (34.6)	3 (0.5)	2 (66.6)
Total	10 001	1570 (15.7)	620	112 (18.1)
Colonoscopy				
I (0–5)	8967 (55.6)	746 (8.3)	578 (60.2)	54 (9.3)
II (6–10)	4575 (28.4)	645 (14.1)	253 (26.4)	45 (17.8)
III (11–15)	1942 (12.1)	425 (21.9)	96 (10.0)	17 (17.7)
IV (16–19)	580 (3.6)	166 (28.6)	31 (3.2)	9 (29.0)
V (20+)	56 (0.4)	30 (53.6)	2 (0.2)	2 (100)
Total	16 120	2012 (12.5)	960	127 (13.2)

* Proportions meeting the primary outcome were not significantly different in the derivation and validation cohorts ($P > 0.05$).

Risk of difficult sedation/high sedation requirement for each procedure type can be estimated for an individual patient by calculating the patient's SCOPE score from Table 4, determining the associated SCOPE class for this score in Table 5 and finding the associated risk in the derivation and validation cohorts. An online SCOPE score calculator has been developed and is available at the following URL: http://www.columbia.edu/~bl114/scope.

DISCUSSION

In this study of 13 711 patients undergoing OGD and 21 763 patients undergoing colonoscopy, we have identified a number of risk factors for difficult sedation and/or high sedation requirement during these procedures. For both OGDs and colonoscopies, we found that younger age, indication for procedure, home benzodiazepine use and home opioid use were associated with difficulty with sedation/high sedation requirements. In addition, several variables were only associated with the primary outcome for each type of endoscopic procedure: for OGD, presence of a fellow, male sex and psychiatric history were associated with this outcome, while for colonoscopy, female sex, BMI <25, tobacco use and other psychoactive medication use were associated with this outcome. We have developed two clinical predictions scores for OGD and colonoscopy based on these associations; these Stratifying Clinical Outcomes Prior to Endoscopy (SCOPE) scores can be used to help endoscopists predict which patients may be difficult to sedate or have high sedation requirements.

Relatively little research has been done in identifying risk factors for difficult-to-sedate patients undergoing endoscopic procedures. One recent study involving 143 patients identified pre-procedure anxiety and chronic psychotropic use as risk factors for patient undergoing moderate sedation with midazolam and fentanyl for OGD and colonoscopy, and found that gender, alcohol abuse, history of sexual abuse or physical abuse and chronic opioid or benzodiazepine use were not risk factors contrary to the investigators' hypothesis.[13] Another study that included 135 patients found that for patients undergoing deep sedation with propofol, pre-procedure anxiety did not correlate with required anaesthesia dose.[14] A study published in 2005 found that pre-procedure anxiety and use of psychotropic drugs or alcohol were associated with an 'adverse endoscopic experience'.[15] An additional study ($n = 773$) investigated BMI, age and gender in relation to CRC screening colonoscopy preparation quality, sedation use, and procedure time and found that decreasing age and female sex were associated with higher doses of sedative medications.[16] A previous study by our group showed that patients with coeliac disease have higher sedative dose requirements during OGD and colonoscopy than those without coeliac

disease.[17] The present study is the largest study to date investigating risk factors for difficult-to-sedate patients during endoscopic procedures, and we have used the results of this analysis to develop and validate a clinical prediction score to assist providers in risk-stratifying patients.

The primary outcome measured in this study was a composite of difficulty with sedation, assessed through analysing endoscopist notes, and high sedation requirement, assessed through analysis of doses of sedative medications received. This composite outcome was chosen because an endoscopist report of difficult sedation or agitation would likely be a specific but insensitive measure, as not all endoscopists take the time to document difficulty with sedation. This, coupled with the fact that this outcome was found to be quite rare (1.0% in OGD, 2.1% in colonoscopy) necessitated the need for another more sensitive outcome. We hypothesised that patients who received the highest doses of sedative medications would be more likely to pose difficultly for the endoscopist administering the medications, with good sensitivity and specificity. The primary outcome was chosen to be a composite of both outcome measures, and a sensitivity analysis was performed solely with the rarer outcome of difficulty with sedation. Some differences were seen between the primary and sensitivity analyses, such as benzodiazepine use not showing significant association with the outcome; however, we believe these are primarily driven by the rarity of the outcome and some of the covariates, making it less likely for the less strongly associated outcomes seen in primary analysis to meet statistical significance in the sensitivity analysis. In addition, secondary analysis using the endpoint of top quintile of sedative medication doses per individual provider showed few differences from the primary analysis, showing that variability between providers' dosing habits was unlikely to be driving the observed associations.

Age was found to be the strongest predictor of difficult/high sedation requirement for both OGD and colonoscopy. This could be due to more judicious use of sedation in older patient on the part of the endoscopist, or due to the previously described inverse correlation of midazolam requirement and age for endoscopic procedures.[18] The association of female sex with the primary outcome for colonoscopy but not for OGD may be explainable by differences in anatomy related to colonoscopy. It has been previously described that female sex is associated with an increased risk of abdominal discomfort during colonoscopy as compared to men,[19] and that females receive higher sedative medication doses for conscious sedation during screening colonoscopy.[16] This is consistent with our findings, and supports the idea that this could be due to increased pain during colonoscopy in females, perhaps due to increased tortuosity of the colon due to female reproductive anatomy, or greater colon length that has been described in women.[20]

It has previously been described that normal weight (BMI $\leq$25) is associated with more difficult colonoscopy as defined by time required for caecal intubation,[21] but to our knowledge this is the first study to find that underweight and normal weight is associated with increased risk of difficult sedation or high sedation requirement for colonoscopy. This phenomenon is likely due to increased discomfort during the procedure owing to less mesenteric fat to pad the manipulation of the colon by the colonoscope, and greater tortuosity of the colon in thinner individuals.

Chronic use of opioids and benzodiazepines, the same medications used for conscious sedation in this population, leads to tolerance to these medications.[22, 23] Patients who take other psychoactive medications besides opioids and benzodiazepines (i.e. anti-psychotics and anti-depressants) or have a psychiatric history may suffer from more significant anxiety or visceral hypersensitivity than those who do not, which may make them more difficult to sedate.

One potential limitation of this study is that patients who received anaesthesiologist-administered sedation were not included in the analysis. Over the study period, approximately 12.5% of procedures were performed utilizing anaesthesia services, including patients with cardiovascular or other comorbidities that mandated additional monitoring. At this institution, the decision to utilise anaesthesia services is at the discretion of the endoscopist, and must be scheduled in advance; this could be due to a variety of reasons include previous difficulty with sedation, significant cardiopulmonary disease, anxiety, patient request and others. Because of the increase in the use of anaesthesia services in routine procedures in recent years, we consider that the SCOPE score may help define those with greater sedation needs and who may benefit from the use of anaesthesia services, beyond those in whom use of anaesthesia services is prudent due to other factors. Another limitation is the presumed presence of practitioner variability in rates of documentation of qualitative descriptors such as agitation, discomfort, or difficulty with sedation, which were used as endpoints in the study. One potentially important risk factor that was not studied as data were unavailable was alcohol use, which affects benzodiazepine tolerance[24] and could lead to high sedation require-

ments for endoscopic procedures as well. Strengths of this study include its large study population and validation of the clinical prediction scores showing good agreement with derivation data.

In conclusion, we have identified several risk factors for difficult sedation for endoscopic procedures and developed a clinical prediction score, the SCOPE score, which can be used to risk-stratify patients for agitation or high sedation requirement. Future studies should investigate why certain populations are more difficult to sedate.

AUTHORSHIP

Guarantor of the article: Benjamin Lebwohl.

Author contributions: Eric D. Braunstein: study design, acquisition of data, analysis and interpretation of data, statistical analysis and drafting of the manuscript. Richard Rosenberg, Frank Gress and Peter H.R. Green: analysis and interpretation of data, critical revision of the manuscript. Benjamin Lebwohl: study concept and design, drafting of the manuscript and critical revision of the manuscript. All authors approved the final version of this manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge Jimmy Duong for assistance with statistical methodology in conjunction with the Irving Institute for Clinical and Translational Research and the College of Physicians and Surgeons Scholarly Projects Program at Columbia University Medical Center.

Declaration of personal interests: None.

Declaration of funding interests: Dr Lebwohl is supported by the National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040). Eric Braunstein is supported by the Columbia University College of Physicians and Surgeons Scholarly Projects Program Friedman Grant.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. List of generic and brand name medications for home medication use.

Table S2. Sensitivity analysis: multiple logistic regression analysis using the endpoint of difficult sedation/agitation mentioned in the procedure note.

Table S3. Multiple logistic regression analysis using the endpoint of high sedation requirement defined by being in the top quintile of both benzodiazepine and opioid doses, with quintiles calculated per individual provider.

REFERENCES

1. Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy, Lichtenstein DR, Jagannath S, *et al.* Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008; **68**: 815–26.
2. Yacavone RF, Locke GR 3rd, Gostout CJ, *et al.* Factors influencing patient satisfaction with GI endoscopy. *Gastrointest Endosc* 2001; **53**: 703–10.
3. Khiani VS, Soulos P, Gancayco J, *et al.* Anesthesiologist involvement in screening colonoscopy: temporal trends and cost implications in the medicare population. *Clin Gastroenterol Hepatol* 2012; **10**: 58–64.e1.
4. Liu H, Waxman DA, Main R, *et al.* Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. *JAMA* 2012; **307**: 1178–84.
5. Inadomi JM, Gunnarsson CL, Rizzo JA, *et al.* Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. *Gastrointest Endosc* 2010; **72**: 580–6.
6. Vargo JJ, Bramley T, Meyer K, *et al.* Practice efficiency and economics: the case for rapid recovery sedation agents for colonoscopy in a screening population. *J Clin Gastroenterol* 2007; **41**: 591–8.
7. Wang A, Hoda KM, Holub JL, *et al.* Does level of sedation impact detection of advanced neoplasia? *Dig Dis Sci* 2010; **55**: 2337–43.
8. Paspatis GA, Tribonias G, Manolaraki MM, *et al.* Deep sedation compared with moderate sedation in polyp detection during colonoscopy: a randomized controlled trial. *Colorectal Dis* 2011; **13**: e137–44.
9. Dominitz JA, Baldwin LM, Green P, *et al.* Regional variation in anesthesia assistance during outpatient colonoscopy is not associated with differences in polyp detection or complication rates. *Gastroenterology* 2013; **144**: 298–306.
10. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* 2013; **173**: 551–6.
11. McAuley D. GlobalRPh. *Opioid Converter*. 2013. Available at: http://www.globalrph.com/narcoticonv.htm. Accessed June 11, 2013.
12. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med* 2004; **23**: 1631–60.
13. Bal BS, Crowell MD, Kohli DR, *et al.* What factors are associated with the difficult-to-sedate endoscopy patient? *Dig Dis Sci* 2012; **57**: 2527–34.
14. Chung KC, Juang SE, Lee KC, *et al.* The effect of pre-procedure anxiety on sedative requirements for sedation during colonoscopy. *Anaesthesia* 2013; **68**: 253–9.
15. Pena LR, Mardini HE, Nickl NJ. Development of an instrument to assess and predict satisfaction and poor

tolerance among patients undergoing endoscopic procedures. *Dig Dis Sci* 2005; **50**: 1860–71.
16. Czwornog J, Austin GL. Body mass index, age, and gender affect prep quality, sedation use, and procedure time during screening colonoscopy. *Dig Dis Sci* 2013; **58**: 3127–33.
17. Lebwohl B, Hassid B, Ludwin S, *et al.* Increased sedation requirements during endoscopy in patients with celiac disease. *Dig Dis Sci* 2012; **57**: 994–9.
18. Bell GD, Spickett GP, Reeve PA, *et al.* Intravenous midazolam for upper gastrointestinal endoscopy: a study of 800 consecutive cases relating dose to age and sex of patient. *Br J Clin Pharmacol* 1987; **23**: 241–3.
19. Elphick DA, Donnelly MT, Smith KS, *et al.* Factors associated with abdominal discomfort during colonoscopy: a prospective analysis. *Eur J Gastroenterol Hepatol* 2009; **21**: 1076–82.
20. Saunders BP, Fukumoto M, Halligan S, *et al.* Why is colonoscopy more difficult in women? *Gastrointest Endosc* 1996; **43**: 124–6.
21. Anderson JC, Messina CR, Cohn W, *et al.* Factors predictive of difficult colonoscopy. *Gastrointest Endosc* 2001; **54**: 558–62.
22. Miller LG, Greenblatt DJ, Barnhill JG, *et al.* Chronic benzodiazepine administration. I. Tolerance is associated with benzodiazepine receptor downregulation and decreased gamma-aminobutyric acidA receptor function. *J Pharmacol Exp Ther* 1988; **246**: 170–6.
23. Williams JT, Ingram SL, Henderson G, *et al.* Regulation of mu-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev* 2013; **65**: 223–54.
24. Cook PJ, Flanagan R, James IM. Diazepam tolerance: effect of age, regular sedation, and alcohol. *Br Med J (Clin Res Ed)* 1984; **289**: 351–3.