Research Article

Antispasmodic medications may be associated with reduced recovery during inpatient rehabilitation after traumatic spinal cord injury

Eric R. Theriault^{1*}, Vincent Huang^{2*}, Gale Whiteneck³, Marcel P. Dijkers^{2,4}, Noam Y. Harel^{2,5}

¹New York Institute of Technology, Department of Physical Therapy, Old Westbury, NY, USA, ²Icahn School of Medicine at Mount Sinai, Department of Rehabilitation Medicine, New York, NY, USA, ³Craig Hospital, Research Department, Englewood, CO, USA, ⁴Department of Physical Medicine and Rehabilitation, Wayne State University, Detroit, MI, USA, ⁵James J. Peters VA Medical Center, Spinal Cord Damage Research Center, Bronx, NY, USA

Objective: To determine whether antispasmodic medications are associated with neurological and functional outcomes during the first year after traumatic spinal cord injury (SCI).

Design/Methods: Retrospective analysis of prospectively collected data from six inpatient SCI rehabilitation centers. Baseline-adjusted outcomes at discharge and one-year follow-up were compared using analysis of covariance between patients who received antispasmodic medication on at least 5 days during inpatient rehabilitation and patients who did not.

Outcome measures: Rasch-transformed motor subscore of the Functional Independence Measure (FIM); International Standards for Neurological Classification of Spinal Cord Injury motor scores, grade, and level.

Results: Of 1,259 patients, 59.8%, 35.4%, and 4.8% were injured at the cervical, thoracic, and lumbosacral levels, respectively. 65.6% had motor complete injury. Rasch-transformed motor FIM score at admission averaged 23.3 (95% confidence interval (CI) 22.4–24.2). Total motor score averaged 39.2 (95% CI 37.8–40.6). 685 patients (54.4%) received one or more antispasmodic medications on at least 5 days. After controlling for demographic and injury variables at admission, Rasch-transformed motor FIM scores at discharge were significantly lower ($P = 0.018$) in patients receiving antispasmodic medications than in those who did not. This trend persisted in secondary analyses for cervical, thoracic, and lumbosacral subgroups. Multivariate regression showed that receiving antispasmodic medication significantly contributed to discharge motor FIM outcome. At one-year follow-up, no outcomes significantly differed between patients ON or OFF antispasmodics.

Conclusions: Antispasmodic medications may be associated with decreased functional recovery at discharge from inpatient traumatic SCI rehabilitation. Randomized prospective studies are needed to directly evaluate the effects of antispasmodic medication on recovery.

Keywords: Muscle spasticity, Spinal cord injuries, Rehabilitation, Muscle relaxants

Introduction

Spasticity represents one symptom of the upper motor neuron syndrome, characterized by exaggerated tendon stretch reflexes and involuntary muscle spasms.¹ Spasticity affects roughly two thirds of individuals with spinal cord injury (SCI).^{2,3} However, only a minority of those individuals report that spasticity

significantly decreases quality of life, most often via painful spasms and decreased mobility.^{1,3–7} Qualitative evidence suggests that clinicians may at times prescribe medications for *signs* of spasticity without sufficient regard to patient complaints of detrimental *symptoms* of spasticity.⁸ Whether this potentially unnecessary administration of antispasmodics affects outcomes in acute SCI is unknown.

Recovery from acute SCI and other injuries to the central nervous system is determined partly by neural plasticity. In turn, neural plasticity depends largely on

Correspondence to: Noam Y. Harel, James J. Peters VA Medical Center, 130 West Kingsbridge Road, 7A-13G, Bronx, NY, 10468; 718-584-9000 x1742. Email: noam.harel@mssm.edu

*These authors contributed equally.

neural activity.^{9,10} Antispasmodic medications exert their effects by facilitating inhibitory neural networks.^{11,12} Therefore, we hypothesized that antispasmodic medications may impede recovery from acute SCI by decreasing neural activity. To investigate this, we conducted a retrospective analysis of data obtained prospectively in the SCIR rehab study to determine whether administration of antispasmodic medications during acute inpatient rehabilitation is associated with neurological and functional outcomes at discharge and one year after injury.

Methods

SCIR rehab

We used data collected as part of the SCIR rehab study, which prospectively tracked patient demographic and injury characteristics, treatments and therapies delivered across all rehabilitation disciplines, and outcomes at discharge and at one year after injury in patients with traumatic SCI at 6 acute SCI rehabilitation centers.^{13–16} Consecutive patients who had incurred a traumatic SCI, were older than 12 years of age, and were admitted for initial rehabilitation between the fall of 2007 and December 2009 were eligible. Those who, after acute hospitalization, had received greater than 2 weeks of rehabilitation in another facility or greater than 1 week of treatment in a non-SCI unit were excluded. Institutional Review Board approval was in place at all centers, and informed consent/assent of all patients (or their parents/guardians) was obtained at enrollment. One thousand three hundred seventy-six patients (91.0% of eligible patients) consented.¹⁶ Data were collected by means of medical record abstraction by trained medical record technicians, download of medication records, electronic record keeping by nurses and therapists of treatments administered, interviews, and in-person examinations by therapists and physicians.

Medication classification

Of 1,376 patients enrolled, medications were not recorded for 117 (8.5%)—these cases were excluded from this analysis, resulting in a sample size of 1,259. Type, dosage, and time of all medications administered were downloaded from the hospital electronic records system (or for one center's patients before it acquired an electronic system, abstracted from written records). The major centrally acting antispasmodics included GABAergic (baclofen and benzodiazepines), alpha-2-adrenergic (tizanidine and clonidine), and other (carisoprodol, cyclobenzaprine, metaxalone, methocarbamol) medications. Narcotics, cannabinoids, ketamine, anti-epileptic drugs, peripherally acting antispasmodics,

and non-benzodiazepine sleeping agents were not classified as antispasmodics. The full list of antispasmodic medications is given in Table 1.

Outcomes

The main outcomes were baseline-adjusted motor independence (motor subscale of the Functional Independence Measure [FIM]), as well as neurological grade, level, total, and upper (UEMS) and lower (LEMS) extremity motor scores according to the International Standards for the Neurological Classification of SCI (ISNCSCI).¹⁷ FIM outcomes were collected by certified therapists and nurses at admission and discharge, and by trained research assistants, mostly using telephone interview, at one-year follow-up. To improve metric properties for statistical analysis, FIM data were Rasch-transformed into scores on a continuous interval scale.¹⁶ ISNCSCI outcomes were assessed by attending physicians specialized in SCI.

Statistical analysis

Patients were dichotomized into ON or OFF groups according to whether they received doses on 5 or more days during admission. Days receiving medication was defined based on the single antispasmodic medication administered on the largest number of days during admission. Primary analyses compared outcomes at

Table 1 Antispasmodic medications administered. Number of patients (and percent of the sample) receiving the listed medications on 5 or more days during inpatient rehabilitation.

	No.	%
Benzodiazepines		
lorazepam	195	15.5
diazepam	165	13.1
clonazepam	128	10.2
alprazolam	122	9.7
midazolam	48	3.8
temazepam	40	3.2
clorazepate	5	0.4
chlordiazepoxide	1	0.1
flurazepam	1	0.1
triazolam	1	0.1
Other GABA agonists		
baclofen	516	41.0
phenobarbital	2	0.2
Alpha-2 agonists		
tizanidine	109	8.7
clonidine	57	4.5
Other classes		
cyclobenzaprine	92	7.3
metaxalone	59	4.7
methocarbamol	22	1.7
carisoprodol	3	0.2
Total patients	685	54.4
Total courses of medication	1,566	
Average courses per patient	2.3	

discharge from acute rehabilitation and at one-year follow-up in patients ON or OFF antispasmodic medication. Secondary analyses stratified patients into three groups by level of injury at admission (cervical, thoracic, or lumbosacral). The Mann-Whitney *U* or Kruskal-Wallis Test was used to compare baseline characteristics measured on an ordinal scale, or for interval data that did not have a normal distribution. Although the key outcome data did not fit a normal distribution (based on the Kolmogorov-Smirnov test), the samples were large and similar in size. Therefore, to properly adjust for differences in baseline characteristics, univariate analysis of covariance (ANCOVA) was used. Covariates were injury etiology, age, sex, race/ethnicity (white, black, Latino, or other), Rasch-transformed motor FIM score, ISNCSCI UEMS and LEMS, injury level, and ISNCSCI grade, all at rehabilitation admission. Furthermore, a term reflecting interaction between injury level and ISNCSCI grade was used as an additional ANCOVA covariate. For calculating means and other statistical parameters, grade was coded as A = 1, B = 2, C = 3, D = 4, E = 5. Level was coded 1–30, with C1 = 1, T1 = 9, S5 = 30. Note that due to incomplete data, the number of patients included in the ANCOVA analyses was less than 1,259. Bonferroni corrections were applied to secondary analyses. To compare relative contributions of the covariates to discharge Rasch-transformed motor FIM scores, multivariate linear regression analyses were calculated using either dichotomous ON/OFF antispasmodic medication status, or the log-transformed number of days receiving the most-used antispasmodic medication. Injury etiology, age, sex, race/ethnicity, Rasch-transformed motor FIM, ISNCSCI UEMS and LEMS, ISNCSCI level, and ISNCSCI grade upon rehabilitation admission were entered into the regression model. All analyses were performed using SPSS version 22 (IBM).

Results

Patient characteristics (Table 2, Fig. 1)

The 1,259 patients included in the analysis were admitted to inpatient rehabilitation an average of 30.4 days post-SCI (range 2–275 days). The average age was 37.8 (range 12–88). 1,027 (81.6%) were male. 69.4% were white, 22.6% were black. 48.4%, 22.1%, 14.5%, and 11.0% sustained traumatic SCI because of motor vehicle accident, fall, sports, and violence, respectively. Neurological examination according to ISNCSCI criteria revealed that 59.8%, 35.4%, and 4.8% were injured at the cervical, thoracic, and lumbosacral level, respectively. In terms of completeness of injury, 49.8% were ISNCSCI grade A at rehabilitation

Table 2 Demographic and clinical characteristics at inpatient rehabilitation admission.

Characteristics	No.	%
Sex		
Male	1,027	81.6
Female	232	18.4
Race/ethnicity		
White	874	69.4
Black	284	22.6
Latino	40	3.2
Other	61	4.8
Mechanism		
MVA	609	48.4
Fall	278	22.1
Sports	182	14.5
Violence	138	11.0
Other	52	4.1
Level		
Cervical	753	59.8
Thoracic	446	35.4
Lumbosacral	60	4.8
Grade (all)		
A	627	49.8
B	199	15.8
C	233	18.5
D	200	15.9
	Mean	SD
Age (range)	37.8 (12–88)	17.1
Days since injury (range)	30.4 (2–275)	26.7
Total Motor score	39.2	24.7
UEMS	30.7	19.0
LEMS	8.6	14.7
Rasch-transformed motor FIM	23.3	16.2

MVA, motor vehicle accident.

admission, 15.8% were grade B, 18.5% grade C, and 15.9% grade D. The median raw motor FIM score at admission was 21 (mean 23.7), whereas the median Rasch-transformed motor FIM score was 28.0 (mean 23.3). Patients with thoracic level injury were more likely to have a complete injury ($P < 0.0005$, Kruskal-Wallis test) and higher Rasch-transformed motor FIM

Figure 1. ISNCSCI severity grade by injury level at rehabilitation admission.

Number of patients per group in parentheses.

Table 3 Baseline demographic and clinical characteristics by receipt of at least one antispasmodic medication on at least 5 days.

Characteristics	MEDICATION STATUS				P-value
	ON		OFF		
	No.	%	No.	%	
Sex					
Male	553	53.8	474	46.2	0.400
Female	132	56.9	100	43.1	
Race/ethnicity					
White	503	57.6	371	42.4	0.001
Black	138	48.6	146	51.4	
Latino	18	45.0	22	55.0	
Other	26	42.6	35	57.4	
Level					
Cervical	483	64.1	270	35.9	<0.0005
Thoracic	179	40.1	267	59.9	
Lumbosacral	23	38.3	38	61.7	
Grade					
A	332	53.0	295	47.0	0.205
B	132	66.3	67	33.7	
C	150	64.4	83	35.6	
D	71	35.5	129	64.5	
	Mean	95% CI	Mean	95% CI	
Age	38.5	37.2–39.7	36.9	35.5–38.4	0.017
Total Motor score	32.0	30.2–33.9	48.1	46.3–50.1	<0.0005
UEMS	25.0	23.6–26.5	37.5	36.1–38.9	<0.0005
LEMS	7.0	6.0–8.0	10.7	9.3–12.0	<0.0005
Rasch-transformed motor FIM	18.6	17.4–19.8	28.9	27.7–30.1	<0.0005

scores ($P < 0.0005$, Kruskal-Wallis test) than those with cervical level injury. There was no difference between sexes in injury grade, level, or functional independence. Length of stay averaged 54 days (range 2–325 days, median 43).

Medications

Six hundred eight-five (54.4%) of the patients received a specific antispasmodic medication on 5 or more days during rehabilitation (Table 1). Among these patients, specific antispasmodic medications were administered on 5 or more days 1,566 times, an average of 2.3 medication courses per patient. Baclofen and benzodiazepines comprised the majority of these courses. Patients receiving antispasmodic medications (“ON” group) were slightly older than those who did not (“OFF” group) (38.5 years vs 36.9 years; $P = 0.017$, Mann-Whitney U test) (Table 3). Sex ratio did not differ between the ON and OFF groups. Whites were more likely to receive antispasmodic medication (57.6%) than non-whites (47.3%) ($P = 0.001$, Mann-Whitney U test). Patients with cervical injuries were more likely to receive such a medication (64.1%) than those with thoracic (40.1%) or lumbosacral (38.3%) injuries ($P < 0.0005$, Kruskal-Wallis test). Consistent with this difference in antispasmodic use by injury level, patients in the ON group had lower Rasch-transformed motor FIM scores (18.6 vs 28.9) and

ISNCSCI total, upper, and lower extremity motor scores at admission ($P < 0.0005$, Mann-Whitney U test).

Outcomes

After adjusting for differences in baseline characteristics (etiology, age, sex, race/ethnicity, Rasch-transformed motor FIM score, ISNCSCI UEMS and LEMS, ISNCSCI level, and ISNCSCI grade), patients ON antispasmodic medication had significantly lower Rasch-transformed motor FIM scores at discharge than patients OFF medication (45.8 vs. 47.0, $P = 0.018$) (Fig. 2). Stratifying patients by level of injury revealed similar trends toward lower discharge FIM in patients ON medication, although these did not reach statistical significance (Fig. 2). At one-year follow-up, baseline-adjusted motor FIM scores did not show significant differences according to receipt of antispasmodic medication, although the trend remained (Fig. 2). Baseline-adjusted ISNCSCI grade, level, and motor scores did not significantly differ between patients ON versus OFF medication at discharge or at one year, except that UEMS at discharge was slightly lower in the OFF group ($P = 0.048$) (Table 4).

To further test the robustness of association between outcomes and receiving antispasmodic medication, we also conducted similar analyses using 10 or 20 days receiving medication as the cutoff, rather than 5 days. Discharge Rasch-transformed motor FIM differences

Figure 2. Baseline-adjusted motor FIM at rehabilitation discharge and 1-year follow-up. A) Discharge; B) 1-year follow-up. Solid bars represent patients receiving specific antispasmodic medications on 5 or more days during admission (Y); patterned bars represent patients receiving antispasmodic medication on 4 or fewer days during admission (N). Error bars represent the 95% CI. * = $P < 0.05$. L-S = lumbosacral.

remained similarly significant in both instances (Table 5). In addition, to compare relative contributions of each predictive factor to discharge Rasch-transformed motor FIM scores, multivariate linear regression analyses were used (Table 6). Whether treating exposure as a dichotomous or a continuous variable, antispasmodic medication significantly contributed to discharge motor FIM outcomes in the regression models.

Discussion

In this retrospective analysis of prospectively acquired data from the SCIRehab study, patients undergoing inpatient rehabilitation for acute traumatic SCI had lower motor FIM scores at discharge if they received systemic antispasmodic medication. This association was maintained after adjusting for differences in

baseline demographic and injury factors. Though strictly correlative, this finding is consistent with our hypothesis that by inhibiting neural activity, antispasmodic medication may impede functional recovery from acute SCI.

The average time to admission for acute inpatient SCI rehabilitation in our study was 30 days, with a median of 23 days. By this time point, the initial period of spinal shock has ended, eventually leading to a spastic state in up to 79% of patients with cervical and 69% of patients with thoracic SCI.^{3,18,19} Many patients arrive at inpatient rehabilitation already prescribed a standing dose of antispasmodic medications. In this study, it is unknown at what rate these (or other types of) medications were continued versus initiated once a patient was admitted to inpatient rehabilitation, because information on medications used during the acute hospitalization was not collected.

The inhibitory nature of antispasmodic medications on neural activity may interfere with mechanisms of recovery after acute neurological injury. For example, neural plasticity after stroke is reduced by excessive GABAergic activity in the peri-infarct region.^{20,21} Antispasmodic medications may reduce response to physical therapy in stroke and SCI.^{22,23} Furthermore, patients taking antispasmodic medications are less likely to demonstrate electrophysiological evidence of active residual nerve connections across spinal injuries.^{24–26}

A 2001 single-center retrospective study found that prescription pain and antispasmodic medication use in ambulatory patients with *chronic* SCI correlated with a lower likelihood of sustained ambulation.²³ However, that study was based on self-report of medication use and ambulation, and was not able to evaluate differences by duration or type of medication administered, or the effects on ISNCSCI or FIM. A separate analysis from the same center identified use of prescription medication for spasticity, pain, sleep, and depression to be an independent risk factor for early mortality after SCI.²⁷

The analysis presented here has the advantage of a large and non-selective sample, prospectively acquired data regarding medication use, and neurological and functional outcome assessments made by experienced clinicians rather than based upon self-report. The associations found, even if not always statistically significant, suggest a potential role played by antispasmodics in limiting recovery after SCI. Although the SCIRehab study collected data between 2007 and 2009, the types of antispasmodic medications administered and the functional and neurological outcomes tracked remain relevant today.

Table 4 Baseline-adjusted ISNCSCI grade, level, and motor scores at discharge and one-year follow-up by receipt of antispasmodics for at least 5 days.

TIME	Drug	No.	Grade	Level	No.	Total Motor Score	UEMS	LEMS
DISCHARGE								
All levels	ON	651	2.2 (2.2–2.2)	9.1 (9.0–9.3)	605	46.3 (45.5–47.1)	34.2 (33.7–34.6)*	12.3 (11.7–12.8)
	OFF	524	2.2 (2.1–2.2)	9.2 (9.0–9.4)	489	46.0 (44.7–46.5)	33.5 (33.0–34.0)*	12.3 (11.7–12.9)
Cervical	ON	460	2.4 (2.4–2.5)	4.8 (4.5–5.0)	427	39.2 (38.1–40.4)	23.9 (23.3–24.5)	15.5 (14.8–16.2)
	OFF	248	2.4 (2.4–2.5)	4.9 (4.6–5.2)	225	38.5 (36.9–40.1)	22.9 (22.0–23.7)	15.8 (14.8–16.8)
Thoracic	ON	170	1.7 (1.6–1.8)	15.0 (14.7–15.2)	159	55.7 (54.8–56.7)	49.9 (49.4–50.3)	5.9 (5.1–6.8)
	OFF	243	1.6 (1.6–1.7)	15.0 (14.8–15.3)	231	54.7 (53.9–55.5)	49.5 (49.1–49.9)	5.3 (4.6–6.0)
Lumbosacral	ON	21	2.7 (2.4–3.0)	21.9 (21.0–22.9)	19	73.1 (69.4–76.8)	50.0 (50.0–50.0)	23.1 (19.4–26.8)
	OFF	33	2.7 (2.5–2.9)	21.2 (20.4–21.9)	33	74.4 (71.6–77.1)	50.0 (50.0–50.0)	24.4 (21.6–27.1)
ONE YEAR								
All levels	ON	156	2.5 (2.3–2.6)	9.7 (8.7–10.7)	147	52.0 (50.0–54.0)	36.8 (35.8–37.8)	15.8 (14.4–17.2)
	OFF	149	2.4 (2.3–2.5)	10.3 (9.3–11.4)	134	51.7 (49.6–53.8)	36.7 (35.6–37.7)	15.6 (14.1–17.0)
Cervical	ON	105	2.6 (2.5–2.8)	5.2 (3.7–6.7)	98	44.7 (41.9–47.5)	26.9 (25.5–28.3)	18.4 (16.6–20.2)
	OFF	69	2.6 (2.4–2.8)	6.0 (4.0–7.9)	62	46.3 (42.7–49.9)	27.2 (25.4–29.0)	19.6 (17.3–21.9)
Thoracic	ON	49	2.1 (1.9–2.3)	15.2 (14.5–16.0)	47	58.8 (56.3–61.3)	49.7 (48.3–51.1)	9.5 (7.6–11.3)
	OFF	67	1.9 (1.7–2.1)	15.5 (14.9–16.1)	60	57.4 (55.2–59.6)	49.4 (48.1–50.6)	8.1 (6.5–9.7)
Lumbosacral	ON	2	3.9 (2.7–5.2)	16.9 (6.6–27.1)	2	88.2 (53.2–123.2)	50.0 (50.0–50.0)	38.2 (3.2–73.2)
	OFF	13	3.5 (3.1–3.9)	22.2 (18.5–26.0)	12	82.5 (69.6–95.3)	50.0 (50.0–50.0)	32.5 (19.6–45.3)

UEMS results at discharge were significantly lower in patients not receiving antispasmodics ($P = 0.048$) (denoted by asterisk). All other results were non-significant after Bonferroni correction. Note that in-person assessment of these measures at one year was incomplete, leading to lower numbers of cases.

Table 5 Rasch-transformed motor FIM by different thresholds for days receiving antispasmodic medications.

Days	Drug	No.	Discharge	P-value	No.	One Year	P-value
≥ 5	ON	651	45.8 (45.2–46.4)	0.018	515	55.6 (54.3–56.9)	0.432
	OFF	524	47.0 (46.3–47.7)		428	56.3 (54.9–57.7)	
≥ 10	ON	581	45.6 (45.0–46.3)	0.002	460	55.5 (54.2–56.8)	0.441
	OFF	594	47.1 (46.4–47.7)		483	56.3 (55.0–57.6)	
≥ 20	ON	486	45.5 (44.8–46.2)	0.002	377	55.6 (54.1–57.1)	0.602
	OFF	689	46.9 (46.4–47.5)		566	56.1 (54.9–57.3)	

Study limitations

The strength of these findings is limited in several ways. First and most importantly, the findings are, strictly speaking, only correlative—no causation can be inferred. Spasticity itself was not measured with any standard tool. Neither were the indications for prescribing medications recorded. Therefore, medications

classified as antispasmodics may have been administered for other conditions such as pain, insomnia, or anxiety. Likewise, medications used for these latter indications are sometimes used to treat spasticity as well. Without direct knowledge of the indications for each prescribed medication, we chose to include in the analysis benzodiazepines and additional medications that

Table 6 Linear regression analysis of contributions made by baseline variables to Rasch-transformed motor FIM at discharge.

	Model: Antispasmodics ON/OFF			Model: Antispasmodics log-days		
	Beta	t	Sig.	Beta	t	Sig.
Antispasmodics	−0.037	−2.285	0.022	−0.042	−2.132	0.033
Grade	0.156	5.759	0.000	0.157	4.941	0.000
Level	0.001	0.029	0.977	−0.024	−0.713	0.476
Etiology	−0.014	−0.893	0.372	−0.016	−0.844	0.399
Age	−0.189	−11.403	0.000	−0.214	−10.568	0.000
Race/ethnicity	−0.015	−1.011	0.312	−0.025	−1.368	0.172
Sex	−0.028	−1.901	0.058	−0.012	−0.651	0.515
Rasch-transformed motor FIM	0.176	6.254	0.000	0.174	5.041	0.000
UEMS	0.585	17.836	0.000	0.605	14.473	0.000
LEMS	0.214	7.751	0.000	0.201	6.291	0.000

Regression models were constructed using antispasmodic medication exposure either as a dichotomous (ON/OFF) or a continuous (log-transformed number of days) measure.

have effects on both spasticity and other symptoms. We specifically excluded narcotics, non-benzodiazepine sleep medications, anti-depressants, and anti-epileptics from our analysis.

Furthermore, retrospective comparison of outcomes in patients who did and did not receive a particular type of medical intervention inevitably introduces bias based on baseline differences between the groups. Patients receiving antispasmodic medication were presumably more spastic, leading this group to have significantly lower motor FIM scores at baseline. Therefore, it is impossible to determine how strongly the lower discharge FIM scores seen in this study derive from medication-associated reduced recovery or from spasticity's direct effects on functional status. Although our statistical analyses adjusted for baseline differences, such adjustment can never equal the power of prospective randomization that leads to groups equal for both measured and unmeasured factors. Ideally, propensity scoring is used to equalize baseline differences, but here key baseline information (most centrally, severity of spasticity and limbs affected) was not available.

As seen in other studies, patients with cervical injuries were more likely to receive antispasmodic medication, resulting in a significant difference between ON and OFF groups in baseline neurological level of injury within the entire study sample. However, similar trends toward association between antispasmodic medication and lower discharge motor FIM scores were seen even when analyzing outcomes by spinal level, although these trends did not reach statistical significance. This trend persisted even in patients with lumbosacral injury, a level at which spasticity should be less of a concern. Contrary to the detrimental correlation with motor FIM outcomes, baseline-adjusted UEMS at discharge were slightly *higher* in patients ON antispasmodics, an unexpected finding given that weakness is a common side effect of antispasmodic medication. However, the effect on total motor scores serves as a better comparison with the effect on motor FIM, since FIM incorporates both upper and lower extremity function.

Although our analysis included a large number of patients and demonstrated statistically significant differences in Rasch-transformed motor FIM scores at discharge, the absolute value of that difference was less than two points. The baseline-adjusted difference at discharge was 2 points on the untransformed motor FIM. The minimum clinically important difference for the untransformed motor FIM subscale has been estimated between 11–17 points in the stroke population, but has not been estimated in SCI.^{28,29} Therefore, although

statistically significant, the results of our retrospective analysis are unlikely to be clinically significant in this study population. Only prospectively acquired data from groups that are equivalent at baseline will more clearly define the size of the effect of antispasmodic medications on clinically meaningful recovery, if any.

Collection of ISNCSCI outcomes at one year post-discharge was limited due to incomplete follow-up with in-person visits—motor scores were recorded in only 22.3% at one-year follow-up. Thus, incomplete data sharply limited the ability to find any statistically significant differences at one year using ISNCSCI motor score outcomes.

The use of a 5-day cutoff to dichotomize patients to the ON or OFF medication groups may seem arbitrary. We chose 5 days for two reasons—this would reduce the chance of classifying a patient into the ON group if he or she received medication for acute anxiety or insomnia on a few days during admission; and this cutoff value resulted in two similar-sized groups. Changing the cutoff value to 10 or 20 days (Table 5) further strengthened the main findings at discharge—that administration of antispasmodic medication is correlated with reduced motor FIM scores.

Ascribing a strictly inhibitory role to antispasmodic medications represents an admittedly simplistic view of spasticity and its treatment. GABAergic medications such as baclofen have been demonstrated to *increase* signaling by inhibitory spinal interneurons, leading to improved spasticity without negative effects on volitional movement.^{11,30,31}

Despite these limitations, our findings suggest that administration of antispasmodic medications may be associated with lower motor functional status after SCI. When spasticity causes pain or disability, treatment is clearly warranted. Physical interventions, including stretching and exercise therapy, are almost universally utilized first, with progression toward systemic and increasingly invasive pharmacological and sometimes surgical approaches as needed.³² The potential disadvantages of medication include side effects, drug-drug interactions, and (as suggested here) non-specific neural inhibition. Over-reliance on pharmacological intervention can lead to inhibition of neural circuits that would otherwise contribute to recovery through activity-dependent plasticity. Therefore, in the absence of spasticity *symptoms* that significantly interfere with mobility, rehabilitation therapies, or quality of life, clinicians should avoid prescribing antispasmodic medications based solely upon recognition of spasticity *signs*.^{8,33} This anecdotal impression of mismatched priorities between physicians and patients is supported by

qualitative surveys of patients with chronic SCI,⁸ but we are unaware of data supporting this claim in the acute setting.

Careful analysis of registry-based data can give insight into issues of clinical importance. In this study, we analyzed data from a six-center, three-year study to investigate the question of whether antispasmodic medications are associated with reduced recovery after SCI. The much larger and longer-running Spinal Cord Injury Model Systems database does not collect information regarding medications or spasticity, preventing its use to address this question. Only prospective, randomized trials will be able to unequivocally determine whether administration of antispasmodic medication plays a causative role in functional and neurological outcomes after SCI. If that is the case, then an approach to SCI rehabilitation that maximizes activity-based therapy and avoids excessive use of pharmacological neural inhibitors may enhance recovery. This principle may also apply to other central nervous system injuries, such as stroke²⁰ and traumatic brain injury.

Conclusion

Retrospective analysis of the SCIREhab multicenter database suggests that use of antispasmodic medications during acute rehabilitation is associated with worse motor FIM outcomes at discharge in patients with acute traumatic SCI, even after adjusting for baseline age, race/ethnicity, injury level, and severity. Only a randomized, prospective study can definitively answer whether antispasmodic medications impede recovery from SCI.

Disclaimer statements

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ORCID

Noam Y. Harel <http://orcid.org/0000-0003-3085-2194>

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