Early Administration of Gabapentinoids Improves Motor Recovery after Human Spinal Cord Injury

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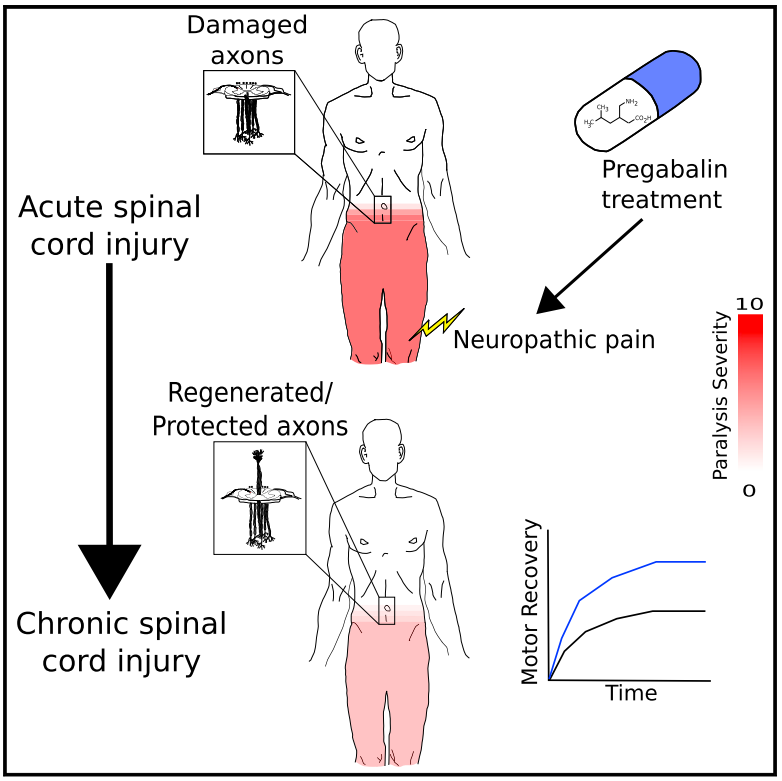
Graphical Abstract



Highlights

- Anticonvulsants were associated with improved motor recovery after spinal cord injury
- The beneficial effect was dependent on administration within 1 month
- Gabapentinoids were identified as the most frequently administered anticonvulsant

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In Brief

In a large observational cohort study, Warner et al. demonstrate that early (not late) administration of anticonvulsants significantly improved motor recovery following acute spinal cord injury. Intervention with anticonvulsants represents a potential pharmacological strategy to improve motor function after spinal cord injury.

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Report

Early Administration of Gabapentinoids Improves Motor Recovery after Human Spinal Cord Injury

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SUMMARY

The anticonvulsant pregabalin promotes neural regeneration in a mouse model of spinal cord injury (SCI). We have also previously observed that anticonvulsants improve motor outcomes following human SCI. The present study examined the optimal timing and type of anticonvulsants administered in a large, prospective, multi-center, cohort study in acute SCI. Mixed-effects regression techniques were used to model total motor scores at 1, 3, 6, and 12 months post injury. We found that early (not late) administration of anticonvulsants significantly improved motor recovery (6.25 points over 1 year). The beneficial effect of anticonvulsants remained significant after adjustment for differences in 1-month motor scores and injury characteristics. A review of a subset of patients revealed that gabapentinoids were the most frequently administrated anticonvulsant. Together with preclinical findings, intervention with anticonvulsants represents a potential pharmacological strategy to improve motor function after SCI.

INTRODUCTION

Andrea Tedeschi and colleagues recently demonstrated that the anticonvulsant pregabalin promotes neural regeneration in the injured mouse spinal cord (Tedeschi et al., 2016). Emerging evidence of pregabalin-induced regeneration builds on existing preclinical literature that has reported neuroprotective effects of other gabapentinoids, such as gabapentin (Emmez et al., 2010; Ha et al., 2008; Kale et al., 2011). In line with these findings, we have previously shown that anticonvulsants are associated with improved motor outcomes following human spinal cord injury (SCI) (Cragg et al., 2016). However, in our previous study, the type of anticonvulsant and the timing of administration that conferred this benefit were unknown. In a "bench-to-bedside" approach, we investigated the effect of the type and timing of anticonvulsant administration on neurological (motor) recovery in the first year post-injury. Together, these preclinical and human studies could inform a randomized clinical trial to determine the efficacy of gabapentinoids as a pharmacological intervention to enhance motor recovery after acute SCI.

RESULTS

There were 83 "early users" of anticonvulsants, 72 "late users," and 470 "non-users," for a total of 625 individuals with a valid categorization (Table 1; Table 2; Figure 1; see Experimental Procedures). In a larger sample than in our previous study (Cragg et al., 2016), longitudinal analysis confirmed that anticonvulsants administered within 1-month post-injury significantly improved motor recovery ($n = 83$ on the drug, $p = 0.019$, for the Drug × Time interaction term). This difference persisted after adjusting for 1-month American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade (injury completeness), motor score, and injury level.

Our next analysis addressed the effects of timing of administration. Unlike administration within the first month, late administration at 3, 6, or 12 months had no significant effect on recovery. Based on this result, late (3-, 6-, or 12-month) users were grouped together for subsequent analyses. Using these groupings, we found that early anticonvulsant use improved motor recovery compared with later administration (Figure 2). Early use conferred a benefit of 6.25 more motor points, on average, over the course of 12 months compared to non-use (Table S1). Early users recovered 4.68 more motor points more than late users. Improved motor recovery in early users remained significant after adjusting for level and severity of injury and 1-month motor scores (Table S1). Including anticonvulsant use also significantly improved the baseline statistical model (Table S2).

Table 1. Cohort Description

Characteristics	n (%)
Total	625
Sex	
Male	507 (81.1)
Female	118 (18.9)
Age at Injury	
Median (IQR)	48 (32)
AIS at 1 Month	
A	239 (38.2)
B	75 (12.0)
C	99 (15.8)
D	212 (33.9)
Neurological Level of Injury at 1 Month	
Upper cervical	176 (28.2)
Lower cervical	139 (22.2)
Thoracolumbar	310 (49.6)
Anticonvulsant Use	
Anticonvulsant use at t = 1 month	83 (13.3)
Anticonvulsant use at t = 3 months	78 (12.5)
Anticonvulsant use at t = 6 months	65 (10.4)
Anticonvulsant use at t = 12 months	42 (6.7)
Total Motor Score at 1 Month	
Median (IQR)	50 (27.0)

IQR, interquartile range; AIS, American Spinal Injury Association Impairment Scale; t, time.

Table 2. Anticonvulsant Group Descriptions

	n (%)		
Characteristics	Non-Users	Late Users	Early Users
Total	470	72	83
Sex			
Male	383 (81.5)	61 (84.7)	63 (75.9)
Female	87 (18.5)	11 (15.3)	20 (24.1)
Age at Injury			
Median (IQR)	47 (32.75)	52.5 (26.0)	48 (30.5)
AIS Grade at 1 Month			
A	190 (40.4)	28 (38.9)	21 (25.3)
B	58 (12.3)	9 (12.5)	8 (9.6)
C	72 (15.3)	14 (19.4)	13 (15.7)
D	150 (31.9)	21 (29.2)	41 (49.4)
Neurological Level of Injury at 1 Month			
Upper cervical	121 (25.7)	23 (31.9)	32 (38.6)
Lower cervical	110 (23.4)	15 (20.8)	14 (16.9)
Thoracolumbar	239 (50.9)	34 (47.2)	37 (44.6)
Total Motor Score at 1 Month			
Median (IQR)	50 (27.75)	50 (22.5)	58 (36.5)
Change in Motor Score from 1 to 6 Months			
Median (IQR)	3 (12.0)	6 (18.0)	8 (16.5)
Change in Motor Score from 1 to 12 Months			
Median (IQR)	4 (15.0)	7 (22.5)	11 (20.0)

IQR, interquartile range; AIS, American Spinal Injury Association Impairment Scale.

The number of times anticonvulsants were administered at each of the four time points (i.e., 0, 1, 2, and 3+), changes in pain (see Experimental Procedures for description of variables), and administration of anti-spasmodics ($p = 0.20$) had no significant effects on motor recovery.

A retrospective chart review on patients from the original analysis ($n = 40$) (Cragg et al., 2016) who had been administered anticonvulsants within 1 month revealed that 33 (83%) received gabapentinoids ($n = 24$ pregabalin, $n = 9$ gabapentin). When comparing only early gabapentinoid users versus non-users using the same longitudinal modeling approach, we found that the beneficial effect remained significant ($p < 0.05$ for greater recovery in motor points over the first year) for this group.

DISCUSSION

In a large and representative sample of acute SCI patients, our findings confirm that anticonvulsants, administered at therapeutic doses for the management of neuropathic pain, enhance motor recovery after acute SCI. Timing of administration was integral for enhanced recovery, with early use (i.e., within 1 month), but not late use (i.e., >1 month), benefiting the recovery of muscle strength. Our new analysis also ruled out one potential mechanism (i.e., reductions in pain) and identified the class of anticonvulsants as gabapentinoids (i.e., pregabalin and gabapentin).

Experimental studies in rodent models have clearly demonstrated a "window of opportunity" for pharmacological interventions to repair the injured spinal cord (Elkabes and Nicot 2014; Wu et al., 2013). The observation of a time-dependent effect in humans (i.e., within 1 month but not later) suggests that anticonvulsants may be directly, through their biological activity in the CNS, benefiting motor outcomes after SCI. This is bolstered by the observation that changes in pain had no effect, discounting the theory that anticonvulsants are impacting motor outcomes indirectly through pain relief.

Both regeneration and neuroprotection may be important mechanisms to consider underlying the direct effects of anticonvulsants. First, a recent study reported that the administration of pregabalin 1 hr post-injury resulted in an increased number of regenerating axons rostral to the lesion site (Tedeschi et al., 2016). Further, delaying pregabalin treatment for weeks showed anatomical regeneration of axons, but to a lesser extent, with the rationale that axons may be set too late in their growth state (when the glial scar is already formed) (Tedeschi et al., 2016). This beneficial effect was mediated via blocking $\alpha 2$-δ subunits, for which both pregabalin and gabapentin have a high affinity and selectively bind (Gee et al., 1996; Gong et al., 2001). Second, the neuroprotective effects of gabapentinoids have also been widely demonstrated across a number of animal models of neurological conditions, including SCI (Emmez et al., 2010; Ha et al., 2008; Kale et al., 2011). Neuroprotection has been attributed to various other biological actions of gabapentinoids in the CNS (e.g., changes in glutamate metabolism) (Ha et al., 2008).

That gabapentinoids have the potential to improve function via multiple pathways (i.e., regeneration and neuroprotection) may make them suitable candidates for translation into humans. First,

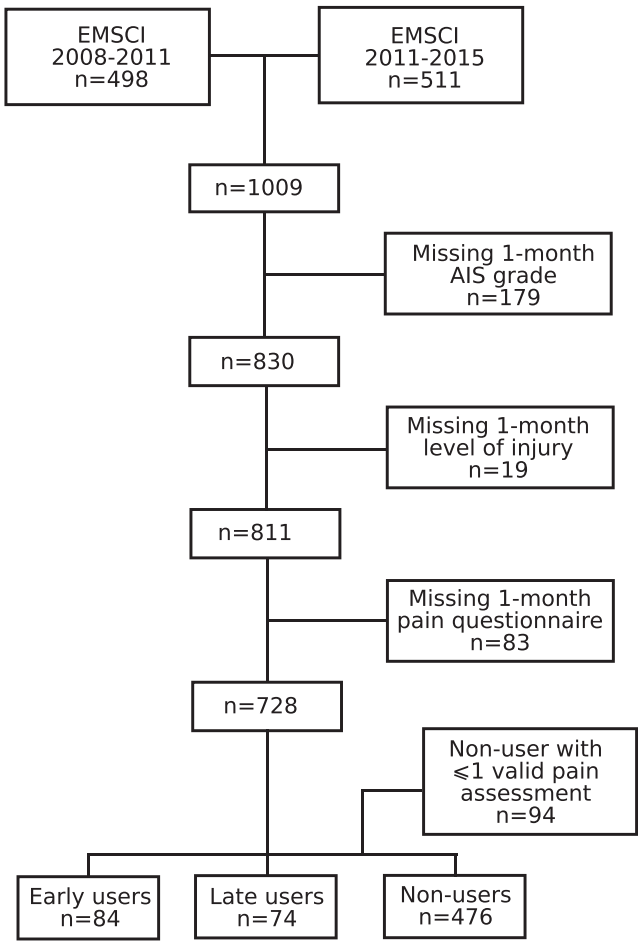

Figure 1. Participants Included from the EMSCI Dataset
EMSCI, European Multi-Center Study about Spinal Cord Injury; AIS, ASIA impairment scale.

a regenerative window could mean a longer opportunity for delivery, outside the boundary of conventional neuroprotective interventions (e.g., minutes to hours post-injury). This has important clinical implications, increasing the number of patients that can be treated based on later admission times to acute care facilities. The translational potential of gabapentinoids is also enhanced by the fact that they have an established safety profile in the acute stage of SCI. A clinical trial to assess the efficacy of gabapentinoids to improve motor outcomes after SCI could administer gabapentin and pregabalin in routine clinical dosages as related to the management of pain without changing practice guidelines for neuropathic pain, simply by shifting to a prophylactic management regime. The time from discovery to translation is long and arduous, and it means that even existing preclinical therapies currently being tested in animal models are years away from applications in humans (Ramer et al., 2014). Gabapentinoids offer a rare and exciting opportunity to repurpose a medication already in use, which, in turn, circumvents many of the difficulties of performing early-phase clinical trials in the field of SCI (e.g., expensive and time consuming).

It is well known that nearly every individual sustaining SCI receives multiple types and classes of medications to manage a litany of problems associated with traumatic SCI. Somewhat surprisingly, very little is known to what degree these acute medications have downstream and unintended effects that could be beneficial or detrimental on neurological recovery. This is all the more surprising, in light of the fact that many common medications coincidentally administered in early phases of SCI have been tested in experimental models (Hirsch and Hunot 2009; Wang et al., 2015; Melzer et al., 2008). As an example, phenytoin (trade name, Dilantin), a potent sodium channel blocker and anticonvulsant administered for neuropathic pain in the 1990s (i.e., pre-dating gabapentinoids), has demonstrated comparable benefits to other neuroprotective treatments currently in clinical trial (e.g., Riluzole) (Schwartz and Fehlings, 2001). Some medications have demonstrated detrimental effects. This includes opioids, which have been shown to limit the recovery of locomotor function (Hook et al., 2009, 2011; Woller et al., 2012). This should be considered a major concern, as opioids are ubiquitously administered for pain management in humans sustaining an acute traumatic SCI. That these important preclinical observations have not yet been examined in the context of human SCI points to a failure in translation and potentially missed opportunities to maximize neurological recovery.

A limitation of our study is that we do not have information on exact timing or dosage of anticonvulsant administration within 1 month. Since anticonvulsants were administered for neuropathic pain, we can speculate that dosages are in line with current management guidelines (Guy et al., 2016). Very little information is known about neuropathic pain in the very acute stages of injury. This makes speculation of when the initiation of anticonvulsant administration may have been more difficult. Moreover, outside the scope of the current study, an important and remaining issue is whether anticonvulsant-induced motor recovery results in improved functional outcomes (e.g., ambulation and use of the hands) (Wu et al., 2015). At this point, the observed five- to seven-point improvement in muscle strength based on uncertain dosages and frequency should be interpreted as evidence of a modest change. The next step, which may only be achievable in a clinical trial, would be to determine whether optimizing dosages and timing (within the 1-month time frame) could enhance this effect and, in turn, lead to improvements in function (i.e., the Functional Independence Measure and the Spinal Cord Independence Measure).

In summary, we have provided corresponding evidence in humans that anticonvulsants have beneficial effects on motor recovery after an acute SCI. These effects are time dependent (within 1 month) and primarily related to the application of gabapentinoids. Future studies may be warranted to assess the efficacy of anticonvulsants as a repurposed therapy to enhance motor outcomes after acute SCI.

EXPERIMENTAL PROCEDURES

Our observational cohort study analyzed prospectively gathered data from the European Multi-centre Study about SCI (EMSCI). Further details on the EMSCI database can be found elsewhere (http://www.emsci.org) (Tanadini et al., 2014). The cohort (2007–2011) previously utilized by Cragg et al. was

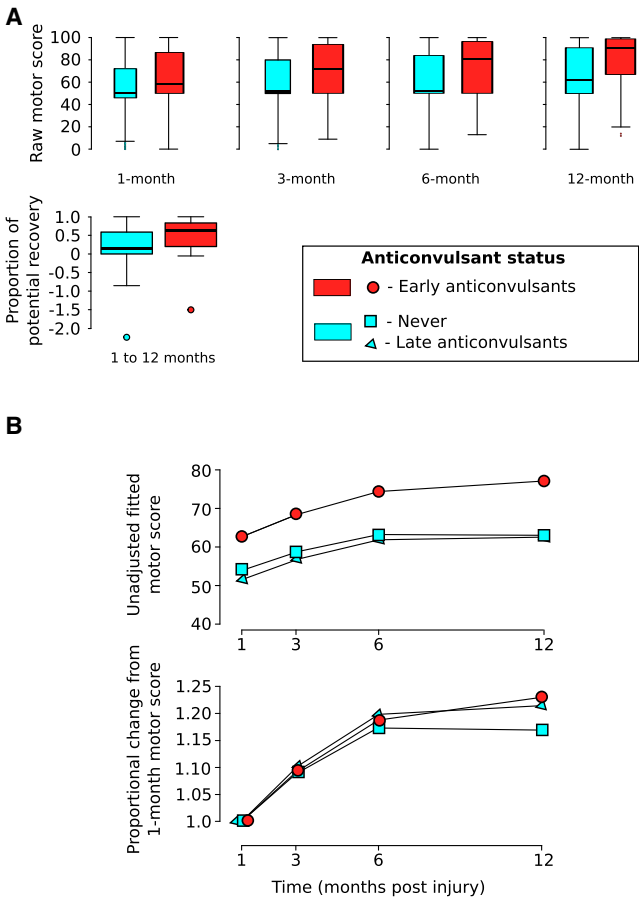

Figure 2. The Effects of Anticonvulsant Administration on Motor Outcomes

(A) The effects of anticonvulsant use (early versus late/none) on motor recovery following SCI at 1, 3, 6, and 12 months. Boxplots show raw data at each time point. Boxplot whiskers indicate the maximum and minimum limits of the data, excluding outliers. Proportion of potential recovery indicates the proportion of "available" recovery (for a total motor score of 100) achieved over 12 months. For example, if an individual had a 1-month motor score of 40, their potential recovery would be 60 points (100 − 40).

(B) The modeled effects of anticonvulsant use on motor recovery following SCI. This model was derived from linear mixed-effects methods, including early users (n = 83), late users (n = 72), and non-users (n = 470). There was a significant Drug × Time interaction (i.e., greater slope or recovery) in early users compared with non-users, even after adjusting for injury characteristics. The unadjusted fitted curve is based on the unadjusted mixed-effects model. The bottom curve depicts the proportion of recovery (relative to 1-month scores) at each time point based on the predicted values of the unadjusted curve.

combined with an updated cohort from 2011. From all EMSCI participants, we included only individuals with a defined level of injury (spinal cord levels C1–T9), an injury severity measure (AIS grades A–D), and pain assessment within 1 month post-injury (Figure 1). The primary outcome variable was total motor score (measure of muscle strength in the upper and lower extremities) as defined by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011). Total motor scores were measured on a scale ranging from 0 to 100, at 1, 3, 6, and 12 months post-injury.

Pain characteristics, descriptors, classifications, and medications were tracked post-injury via a questionnaire by trained examiners. Specific data extracted included medication type and timing, pain intensity (numeric rating scale, representing the average intensity in the last week prior), and pain classification (nociceptive or neuropathic). Data regarding dosages, reason for administration, and frequency of administration within the time periods were not available. However, anticonvulsants—specifically, gabapentin and pregabalin—are currently the frontline treatments for neuropathic pain after SCI. Both drugs are administered at a base dose, with flexible dosing increases dependent on effectiveness and tolerance (Guy et al., 2016). Three groups were defined: "non-users" (i.e., never administered anticonvulsants with at least two valid assessments), "late users" (i.e., administered anticonvulsants but not within the 1-month time point), and "early users" (i.e., administered anticonvulsants within the 1-month time point). As a proxy for frequency of use, we examined the number of times anticonvulsant administration was recorded (i.e., taken at how many of the four time points: zero, one, two, or three or more times). Regarding pain intensity, three measures were derived: (1) pain intensity at each time point, (2) the average pain intensity across the four time points, and (3) changes in pain intensity scores over the four time points.

Potential confounding variables examined included: age at injury, sex, 1-month motor scores, neurological level of injury, and injury severity according to the AIS. In addition, the use of anti-spasmodics was examined as potential confounder. To account for the longitudinal data and potential confounders, multivariable analyses were performed using linear mixed-effects regression (LMER) models (R package: lme4). To assess differences between groups, we examined Covariate × Time interactions. We plotted the fitted (predicted) values from the LMER (Figure 2). For each group, we also took the fitted values from the LMER model at each time point and plotted the proportional increase in motor score relative to the 1-month score (Figure 2). RStudio statistical software, version 0.99.484, was used for all analyses (R Core Team 2015).

SUPPLEMENTAL INFORMATION

Supplemental Information includes three tables and can be found with this article online at http://dx.doi.org/10.1016/j.celrep.2017.01.048.

AUTHOR CONTRIBUTIONS

F.M.W. contributed to the conception and design of the study, the data analysis, and drafting the manuscript and figures. J.J.C. contributed to the conception and design of the study, the data analysis, and revising the manuscript. C.R.J. contributed to the design of the study and revising the manuscript. A.C. contributed to the design of the study, revising the manuscript, and data acquisition. J.K.K. contributed to the conception and design of the study, revising the manuscript, and data acquisition. EMSCI Sites, F.R., N.W., M.S., D.D.M., and C.S. contributed to data acquisition and revising the manuscript.

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