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The Association Between Medication Use and Cognitive Performance in People With SCI

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Purpose/Objective: Polypharmacy is common in people with spinal cord injury (SCI). Given the high rates of medication use, and the complicated side effect profile of many of the medications that are regularly prescribed in people with SCI, we were interested in the association between the use of different classes of medications and cognitive function in these individuals. ***Research Method/Design:*** One-hundred and 73 people with SCI participated in an observational study. Self-reported medications were provided by participants. Participants also completed several cognitive tests designed to capture multiple aspects of cognition (processing speed, attention, working memory, learning, free-recall memory, delayed free recall memory, executive function), as well as a self-report measure that captures participant perceptions of cognitive function. A series of multivariable linear regressions were used to test for associations between medications and the seven measures of cognition. ***Results:*** In general, there was not a robust relationship between medication use and cognitive function; the sole exception was an association between opioid use and subjective cognitive function. There was some preliminary support for an association between medication use, especially benzodiazepine and opioid analgesic use, and poorer cognitive performance. Specifically: Opioid analgesic use was associated with slowed processing speed, worse attention, poorer working memory, poorer executive function and more subjective cognitive complaints; benzodiazepine use was associated with slower processing speed, poorer working memory, and worse executive function; anticonvulsant use was related to worse delayed free recall memory; and the number of medication categories a person with SCI was taking was related to slower processing speed, and worse subjective cognitive function. Antidepressant, cannabis, skeletal muscle relaxant, sedative and stimulant use were not significantly related to cognitive performance, nor to subjective reports of cognitive function. ***Conclusions/Implications:*** Findings did not support a strong relationship between medication use and cognitive function in people with SCI. There is some preliminary support for an association between benzodiazepine use and cognitive performance, but this needs to be confirmed in future research.

Impact and Implications

While the complex medical needs of people with spinal cord injury commonly include complicated medication regimens, little is known about the impact that these medications may have on cognition. Contrary to expectations, in general, there were not strong relationships between medication use and cognitive function in people with SCI. Preliminary support for a significant association between medication use, especially benzodiazepine and opioid analgesic use, and poorer cognitive performance in people with spinal cord injury warrants further study in order to better understand the possible effects of medications on cognition in this population.

Keywords: cognitive function, spinal cord injury, medication use

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Introduction

Spinal cord injury (SCI) is often accompanied by a number of co-occurring conditions, ranging from mood disorders to chronic pain, all of which can significantly impact the health-related quality of life of these individuals (Chiodo et al., 2007; Jensen et al., 2007; Kroll et al., 2007; Noonan et al., 2008). The management of these comorbid conditions can employ multiple treatment modalities including prescription medications; it is common for people with SCI to simultaneously use multiple medications (Chiodo et al., 2007; Goodman et al., 2014; Hatch et al., 2018; Kitzman et al., 2017; Lee et al., 2010; Patel et al., 2017; Rouleau & Guertin, 2011). Indeed, polypharmacy has been identified as a significant threat to health in SCI (Atkins et al., 2014; Goodman et al., 2014; Guilcher et al., 2018; Hatch et al., 2018; Kitzman et al., 2017; Patel et al., 2017; Rouleau & Guertin, 2011). For example, one study indicated that people with SCI (a sample of 175 people that included those with both traumatic an nontraumatic injuries) were prescribed over 19 classes of medications representing over 300 different drugs (Rouleau & Guertin, 2011). In addition, people with SCI are also more likely than age- and sex-matched controls to be prescribed medications from multiple high-risk classes (sedatives, analgesics, narcotics, skeletal, muscle relaxants, antispasmodics, anticonvulsants, antianxiety, and antidepressants; Kitzman et al., 2017). Given these high rates of medication use, and the complicated side effect profile of many of the high-risk classes of medications, we were interested in understanding the impact this medication use has on people with SCI.

Of particular interest is the possibility that medication use is associated with poorer cognitive functioning for people with SCI. Evidence suggests that persons with SCI are 13 times more likely to be cognitively impaired than persons without SCI, although it is unclear which clinical and injury-specific variables predict these impairments (Craig et al., 2017). Compared with non-SCI groups, persons with SCI tend to perform lower on measures of memory and executive function and have alterations in brain regions influencing attention, processing speed, and recognition (Bradbury et al., 2008; Cohen et al., 2017; Davidoff et al., 1985; Davidoff et al., 1992; Dowler et al., 1997; Dowler et al., 1995; Hess et al., 2003; Lazzaro et al., 2013; Macciocchi et al., 2013; Nightingale et al., 2020; Roth et al., 1989; Sachdeva et al., 2018; Wilmot et al., 1985). It is also typical for rehabilitation programs to focus on community reintegration, using techniques to improve learning, memory, and communication (Sachdeva et al., 2018). Exploring the factors contributing to this cognitive impairment is therefore essential to understanding and ultimately improving the health-related quality of life in the SCI population. Although there are many confounding factors that could contribute to this cognitive impairment, little is known about the long term effects of medications commonly prescribed within this population on cognitive function.

As mentioned above, many of the common medications that are prescribed for people with SCI postinjury, especially opioid analgesics, skeletal muscle relaxants, antispasmodics, opioid analgesics, sedatives, and benzodiazepines, can have a negative impact on cognitive function. For example, opioid analgesics and skeletal muscle relaxants have been linked to decreased cognitive/adaptive control in humans, a key tenet of cognitive function (van Steenbergen et al., 2017). In addition, a study examining cannabis found that chronic cannabis users had less cognitive capacity to monitor their behaviors and process errors (Hester et al., 2009). Studies have also found that benzodiazepines have a negative impact on cognitive control (i.e., processing speed, attention and executive functioning; Leicht et al., 2013). Regardless of these reported significant associations, it is unclear if these associations are clinically meaningful.

There is also evidence that antispasmodics and anticholinergics have a negative impact on cognition. Research in older adults has reported a link between these medications and acute cognitive impairment (on tests of reaction time [RT], attention, delayed nonverbal memory, narrative recall, visuospatial construction, and language but not reasoning, immediate or delayed recall of words nor implicit memory; Ancelin et al., 2006; Campbell et al., 2009; Pasina et al., 2013), as well as evidence that these medication classes can accelerate the onset of dementia (Fox et al., 2011; Fox et al., 2014).

With regard to anticonvulsant medications, the impact on cognition appears to depend on the class of the agent. Specifically, while the older class anticonvulsants appear to have a negative effect on cognition (Sabers et al., 1995), most of the newer anticonvulsants do not appear to impact cognition (Goldberg & Burdick, 2001; Sabers et al., 1995). The exception to this is topiramate (a newer class anticonvulsant), which has a more negative profile than the other newer class anticonvulsants; topiramate appears to have a mild negative effect on attention, psychomotor speed, verbal memory, and verbal fluency (Goldberg & Burdick, 2001).

Studies that have examined antidepressants and their relationship to cognition in those with major depressive disorder have found that antidepressants may be associated with small improvements in at least some aspects of cognitive function (Robinson & Jorge, 2016; Rosenblat et al., 2015). A recent systematic review and meta-analytic report of people with major depression disorder reported that antidepressant use had a positive effect on psychomotor speed and delayed recall (Rosenblat et al., 2015). In addition, meta-analytic data in people with stroke have found that antidepressant treatment is associated with enhanced cognitive recovery, especially when used early in the recovery process (Robinson & Jorge, 2016). Finally, although stimulants are not among the most commonly prescribed medications for people with SCI, stimulants are typically associated with improvements in attention/concentration (Advokat, 2010).

While the above cited evidence would support a negative association between medication use and cognition across a variety of different study populations, the majority of these studies employ small sample sizes, lack meaningful control groups, or employ cognitive tests that are not commonly used to evaluate clinically significant problems (i.e., cognitive tests that rely heavily on processing speed and are utilized in the experimental literature). Thus, more work is needed to better understand the association between medication use and cognitive function, and the clinical significance (if any) of these relationships.

Given that there is evidence for a number of medications (especially opioid analgesics, skeletal, muscle relaxants, analgesics, sedatives, benzodiazepines, antispasmodics, anticholinergics, and the older class anticonvulsants) to have a negative impact on cognitive function in other clinical groups, we were interested in better understanding the association between self-reported medication use and cognition in people with SCI. Specifically, we hypothesized that people with SCI who were taking opioid analgesics, skeletal muscle relaxants, sedatives, benzodiazepines, antispasmodics, anticholinergics, anticonvulsants, or cannabis would have worse performance on cognitive tests, relative to those that were not taking these drugs. We did not expect antidepressant use to impact cognition, as we did not

expect that the small improvements that have been demonstrated in the broader literature to be seen for this sample which did not recruit for a depressive disorder. Furthermore, we expected a negative relationship between the total number of medication categories that an individual reported and their performance on tests of cognitive function. Finally, we expected stimulant use to be associated with a trend for improvement in cognitive function, relative to those who were not prescribed stimulants (that is, while the literature would support an association between stimulant use and cognitive performance, we expected any potential benefit would be small and likely mitigated by other symptoms that are common in SCI [e.g., pain] that have been shown to have a negative impact on cognitive performance).

Method

Participants

Participants were recruited at two academic medical centers. Participants were considered eligible if they had a medically documented spinal cord injury, were fluent in English, capable of providing informed consent, and were willing to complete all study assessments. We excluded inpatients and participants who were currently involved in intensive outpatient physical therapy. Participants were characterized as paraplegic or tetraplegic according to the International Standards for Neurological Classification of SCI (Kirshblum et al., 2011). Community-based recruitment (e.g., study flyers, websites, community events), and hospital-based medical record review, as well as established SCI research registries were used to identify potential study participants. Data were collected in accordance with local Institutional Review Board regulations.

Study Procedures

Detailed study procedures are reported elsewhere (see Carlozzi et al., in press). Briefly, we collected self-reported medication data, as well as conducted several cognitive assessments (these measures were administered in the same fixed order to all study participants). Participants completed a baseline survey session and a follow-up visit. All study participants provided informed consent prior to the commencement of any study-specific activities.

Measures

Demographic Variables

At baseline, participants completed a self-report questionnaire which included questions about the participants' demographics, living/work situation, as well as basic questions about their SCI.

Medications

Medication use was assessed with a medication survey that was part of the demographic form. Respondents were asked to report the name and dosage of prescription medications, over-the-counter medications, and herbal remedies they were currently taking. Given that a medication may fall into several categories, a list of all medications reported by study participants was compiled and reviewed by a physical medicine and rehabilitation practitioner (RB). Medications were assembled into 10 medication categories by drug type (i.e., opioid analgesic, anticonvulsants, tricyclics, SSRIs/SNRIs, benzodiazepines, cannabis, skeletal muscle relaxants, antispasmodics, sedatives, and stimulants) to aid in the examination of medication use on cognitive performance (see Supplemental Table 1 for a detailed breakdown of these categories). The total number of medication categories was aggregated for all medication categories thought to have a negative impact on cognition (i.e., all categories except stimulants) to create a count variable indicating the number of medication categories a participant was actively prescribed/taking.

Objective Cognitive Assessments

During the follow-up visit, participants completed six neuropsychological assessments which are described below. These neuropsychological assessments were selected to parallel those that have been used in other studies of cognition in people with SCI (Carlozzi et al., 2017; Cohen et al., 2017), as well as those that were used as gold standard neuropsychological assessments in the validation work for the NIHTB Cognition Battery (Weintraub et al., 2014). In addition, assessments that did not rely on psychomotor responses were employed, so as not to disadvantage those individuals with SCI that have significant upper limb mobility impairments (AERA, APA, & NCME, 2014; Cicerone et al., 2011). The NIH Toolbox Oral Symbol Digit Test (Weintraub et al., 2013; Weintraub et al., 2014) provides an assessment of processing speed. Participants were required to match numbers with symbols according to a key at the top of the page. They had 120 s to complete as many matches as they could. This measure was completed using the app-based version of the NIHTB Cognition Battery. Scores were calculated by summing the number of correct responses and can range from 0–144; higher scores indicate better processing speed.

The Paced Auditory Serial Addition Test (PASAT; Diehr et al., 1998) provides an assessment of attention. Every 3 s, the participant heard a single digit number, and were asked to add this number to the previous number they heard and provide this sum aloud. Scores were calculated by summing the number of correct responses (maximum of 49); higher scores indicate better attention.

The NIH Toolbox List Sorting Working Memory Test (Tulsky et al., 2014; Tulsky et al., 2013) provides an assessment of working memory. The participant is required to sequence both food and animals in size order. Initially participants are required to sequence items from a single category (one-list version), and then they are required to sequence items across both categories (two-list version). This measure was completed using the app-based version of the NIHTB Cognition Battery. Scores were calculated by summing the total number of correct responses across both the one- and two-list versions (maximum 28); higher scores indicated better working memory.

The California Verbal Learning Test-second edition (CVLT-II; Delis et al., 2000) provides an assessment of verbal learning and memory. Participants are asked to recall as many words as they can from a list of 16 words that is read to them five times. They are then asked to do the same thing for a second list of words which was then followed by a short-delay free recall and a short-delay cued recall of the original list. After 20 min, the participants are asked to provide a long-delay free recall, long-delay cued recall, and recognition trials of the original list. For the purposes of this analysis we examined learning (sum of Trials 1 to 5; range from 0–80), short-delay free recall (range from 0–16), and long-delay free recall raw scores were examined (range from 0–16);

higher scores reflect better memory. We also examined scores on forced choice recognition (range 0–16) to determine if there were any participants with questionable effort on cognitive tests that should be removed from analyses.

The Delis-Kaplan Executive Function System (D-KEFS) color/word interference test (Delis et al., 2001) provides an assessment of executive function (specifically cognitive flexibility and interference). Participants were given a sheet with colors, words (in black ink), and words printed in the wrong color of ink (i.e., the word "red" written in green ink). They were asked to read through each of these three sheets. Scores reflect the number of seconds it took participants to complete reading each sheet. We examined raw scores on the interference sheet (Condition 3, time to completion) where higher scores indicate worse executive function.

The Verbal Fluency Test (Lezak et al., 2004) also provides an assessment of executive function. Participants were given 60 s to name as many words as they can think of that start with a particular letter. Scores were calculated by summing the total number of words produced across three different letter trials (F, A, and S); higher scores indicate better executive function.

Subjective Ratings of Cognition

At the follow-up visit, participants completed a self-report measure of perceived cognitive abilities: the Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Function (Lai et al., 2014) computer adaptive test (CAT). Scores are on a T metric ($M = 50$; $SD = 10$); higher scores indicate better subjective cognitive function.

Data Collection Training and Assurance to Standardized Procedures

Given that this was multisite study, data collectors at both sites follow standardized test administration protocols. Data collectors were trained to administer the NIH Toolbox and other cognitive tests by a neuropsychologist (NEC). Examiners were BA and/or MA-level that completed a certification process prior to the administration of the study assessments. This involved a seminar-based introduction and training for each of the cognitive tests. Examiners were required to practice test administration on at least five "mock" participants. Examiners were then either directly observed (or sent a video-recording) of a mock participant to by the study neuropsychologist (NEC) who reviewed both the administration, as well as at least five scored protocols for accuracy as part of the certification process. Examiners were provided feedback on scoring and administration, and were either certified or instructed to complete additional practice prior to engaging with study participants. In addition, one of the authors (NC) reviewed the first five de-identified test protocols from each examiner, rescored the protocol, and provided feedback about deviations from standard procedures.

Analysis Plan

Participant characteristics were described using mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. Descriptive data for the cognitive tests are reported as both raw and standardized scores. Correlations of medication categories were tested using Phi coefficients. A series of multivariable linear regressions were used to test for associations between medications (i.e., opioid analgesics, anticonvulsants, tricyclics, SSRI/SNRIs, benzo, cannabis related, antispasmodics, skeletal/muscle relaxants, sedatives, and number of medications) and the seven measures of cognition. Raw cognitive test scores were used instead of standardized scores to account for the fact that the cognitive measures adjust for varied demographic factors; by including demographics as covariates, all scores had the same demographic comparisons. First, associations between each medication variable and each cognition outcome were tested in separate models (i.e., 70 separate adjusted models); all models were adjusted for age, gender, education (≥college vs. <college), and injury classification (i.e., tetraplegia vs. paraplegia). Finally, for any cognitive outcome that had a statistically significant relationship with more than one medication variable, multidrug models were performed including each significant medication variable along with age, gender, education, and injury classification. Backward selection was used to iteratively remove any nonsignificant medication variable until all remaining medication variables were significant with $p < .05$. Given that this is the first detailed analysis between medication use and cognition in people with SCI we report findings for both conventional levels of significance, as well as false-discovery rate adjusted p-values with false discovery rate < .15 (Benjamini & Hochberg, 1995). Analyses were performed in SAS V9.4 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Table 1 provides descriptive characteristics of the sample for all variables included in the analyses. Participants had a mean age of 50 years and 36% were female. None of the participants were flagged for suboptimal effort (no participants had scores less than 15 on CVLT forced choice recognition; Denning, 2012; Root et al., 2006). Participants were on a mean of 2.1 medication categories, the most common was SSRI/SNRI (34%) and least common was sedatives (5%). Figure 1 provides a visual representation of the different medication classes that were examined.

Table 2 summarizes results from the multivariable linear regression models. Hypotheses were only partially supported. Specifically, the following findings were consistent with our hypotheses: Opioid analgesic use was consistently associated with poorer cognitive performance on all measures except the measures of learning and memory (learning, short-delay free recall and long-delay free recall auditory memory from the CVLT) and one of the two executive function measures (DKEFS: inhibition); benzodiazepine use was associated with poorer cognitive performance on processing speed (oral symbol digit), working memory (list sorting) and executive function (verbal fluency); anticonvulsant use was related to learning (CVLT: learning) and poorer self-reported cognitive performance (PROMIS cognitive function); antispasmodic use was associated with poorer long delay free recall memory (CVLT); and antidepressant use (SSRI/SNRI, as well as tricyclic use) was not related to cognitive performance (please note that SSRI use was related to subjective reports of cognitive function—PROMIS: cognitive function, but tricyclic use was not). Contrary to hypotheses, cannabis, skeletal muscle relaxants, and sedatives were not related to cognitive performance, nor to subjective reports of cognitive function. We also did not see significant relationships between stimulant medications and any of the cognitive measures (as was hypothesized). Finally, there was a positive relationship between the number of medication categories a person was using and slower processing speed (oral

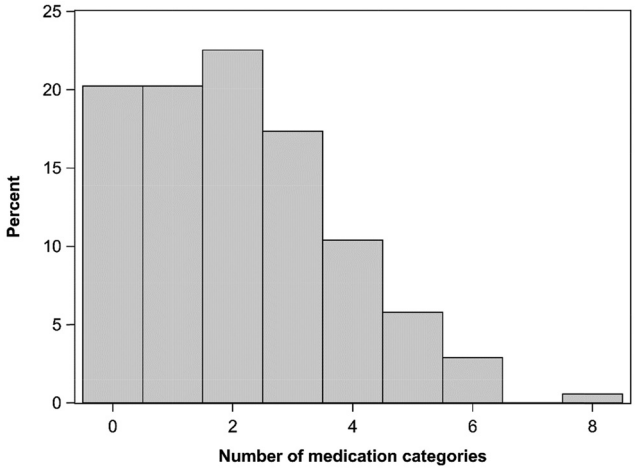
Table 1

Participant Characteristics and Distributions of Medications and Cognitive Measures (n = 173)

Characteristic	Distribution	Range
Participant characteristics		
Age (years), *M* (*SD*)	49.5 (14.65)	19–86
Female, *n* (%)	63 (36)	
Education, *n* (%)		
Grades 9–12, without graduating	4 (2)	
GED	3 (2)	
High school graduate	13 (8)	
Some college credit, no degree	35 (20)	
Associate's degree (e.g., AA, AS)	28 (16)	
Bachelor's degree (e.g., BA, AB, BS)	54 (31)	
Master's degree (e.g., MA, MS, MEng, Med, MSW, MBA)	20 (12)	
Professional degree (e.g., MD, DDS, DVM, JD, LLB)	4 (2)	
Doctorate degree (e.g., PhD, EdD)	5 (3)	
Vocational degree/certificate	6 (3)	
Unknown	1 (1)	
Injury classification, *n* (%)		
Paraplegia	68 (39)	
Tetraplegia	76 (44)	
Unknown/missing	29 (17)	
Comorbidities, *n* (%)		
Other neurological injury (TBI, stroke, other brain injury)	5 (3)	
Mood disorder (depressive disorder, anxiety disorder, bipolar disorder)	7 (4)	
Medications		
Medication categories, *n* (%)		
Opioid analgesics	52 (30)	
Anticonvulsants	56 (32)	
Tricyclics	17 (10)	
SSRI/SNRIs	58 (34)	
Benzodiazepines	39 (23)	
Stimulants	7 (4)	
Cannabis	17 (10)	
Antispasmodics	87 (50)	
Skeletal/muscle relaxants	25 (14)	
Sedatives	10 (6)	
Number of high risk medication categories (those thought to negative impact on cognition)	2.1 (1.68)	
Cognitive outcomes		
Oral Symbol Digit Test (raw score), *M* (*SD*)	74.1 (21.64)	21.0–143.0
Oral Symbol Digit Test (T score), *M* (*SD*)	62.5 (12.6)	32.5–88.5
PASAT (raw score), *M* (*SD*)	37.8 (9.58)	9.0–49.0
PASAT (fully corrected T score), *M* (*SD*)	49.4 (10.67)	20.6–74.2
Listing sorting working memory (raw score), *M* (*SD*)	17.4 (2.77)	11.0–26.0
Listing sorting working memory (fully corrected T score), *M* (*SD*)	50.9 (9.63)	27.0–79.0
CVLT: Learning (raw score), *M* (*SD*)	49.8 (10.05)	19.0–75.0
CVLT: Learning (age- and sex-corrected scaled score), *M* (*SD*)	53.3 (9.73)	25.0–80.0
CVLT: Forced choice recognition (raw score), *n* (%)		
16/16	169 (98)	
15/16	1 (1)	
<15/16	0 (0)	
Unknown	3 (2)	
CVLT: Short-delay free recall (age- and sex-corrected scaled score), *M* (*SD*)	0.2 (0.90)	−2.5–2.0
CVLT: Long-Delay Free Recall (raw score), *M* (*SD*)	10.7 (3.26)	0.0–16.0
CVLT: Long-delay free recall (age- and sex-corrected Z Score), *M* (*SD*)	0.1 (1.01)	−2.5–2.0
DKEFS: Inhibition (raw score), *M* (*SD*)	55.1 (13.99)	28.0–102.0
DKEFS: Inhibition (age-corrected scaled score), *M* (*SD*)	10.9 (2.68)	2.0–16.0
Verbal fluency (raw score), *M* (*SD*)	41.1 (12.97)	16.0–81.0
Verbal fluency (T score), *M* (*SD*)	47.6 (11.1)	21.0–78.0
PROMIS: Cognitive function (T score), *M* (*SD*)	49.4 (9.62)	30.0–68.9
Other covariates		
PROMIS depression, *M* (*SD*)	49.9 (9.8)	34.2–71.1
PROMIS anxiety, *M* (*SD*)	50.6 (9.4)	32.9–73.3
PROMIS pain intensity, *M* (*SD*)	45.9 (7.8)	30.7–62.1

Note. GED = General Educational Development Test; TBI = traumatic brain injury; SSRI = serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; PASAT = Paced Auditory Serial Addition Test; CVLT = California Verbal Learning Test; DKEFS = Delis-Kaplan Executive Function System; PROMIS = Patient Reported Outcomes Measurement Information System.

Figure 1
Distribution of Medication Categories



Note. This figure presents a visual summary of the percentage of study participants reporting medications across different medication categories.

symbol digit) and worse subjective cognitive function (PROMIS: cognitive function). When analyses were corrected for multiple comparisons, the only remaining significant relationship was the positive association between opioid use and self-reported cognitive performance (PROMIS: cognitive function). Full model results including other covariates are included in Supplemental Table 2.

In cases where cognitive measures had relationships with multiple medication categories (see Table 2: processing speed [oral symbol digit], working memory [list sorting], executive function [verbal fluency], and subjective cognitive function [PROMIS: cognitive function]) backward selection was used to determine if one (or more) of the medication categories was driving these relationships. Indicated by bolding, multidrug backward selection models found that benzodiazepine use was the only medication category independently associated with processing speed (oral symbol digit) and working memory (list sorting); additionally, opioid analgesic use was the only medication category independently associated with executive function (verbal fluency) and subjective cognitive function (PROMIS: cognitive function).

Discussion

This is the first study, to our knowledge, that examines the association between different medication classes and cognitive function in persons with SCI. In general, findings did not support a robust relationship between medication use and cognition in people with SCI. The sole exception to this finding was the significant relationship between opioid use and perceived cognition; in this case individuals that reported opioid use also reported poorer subjective cognition.

Regardless, there was some evidence to suggest that medication use, especially benzodiazepine and opioid analgesic use, may be associated with poorer cognitive performance. Specifically, there was some evidence to suggest that opioid analgesic use was associated with slowed processing speed, worse attention, poorer working memory, poorer executive function and more subjective cognitive complaints, but NOT with delayed recall memory. In addition, when

Table 2
Summary of Regression Results of Medication Predicting Cognitive Outcomes (β and 95% Confidence Intervals Shown)

Medication	Cognitive outcome								
	Oral symbol digit test	PASAT	Listing sorting working memory	CVLT: Learning	CVLT: Short-Delay free recall	CVLT: long-Delay free recall	DKEFS: Inhibition	Verbal fluency	PROMIS: Cognitive function
Opioid analgesics	−6.47 [−12.77, −0.16]*	**−4.50 [−7.67, −1.34]***	−0.93 [−1.83, −0.04]*	−2.47 [−5.38, 0.43]	−0.38 [−1.25, 0.49]	−0.70 [−1.67, 0.26]	1.79 [−2.48, 6.05]	**−4.51 [−8.70, −0.31]***	**−6.03 [−8.99, −3.06]*†**
Anticonvulsant	0.02 [−6.25, 6.29]	−0.86 [−4.03, 2.31]	−0.31 [−1.20, 0.58]	**3.49 [0.65, 6.33]***	0.60 [−0.25, 1.46]	0.16 [−0.79, 1.11]	1.27 [−2.86, 5.41]	−2.59 [−6.79, 1.60]	−3.97 [−7.00, −0.94]*
Tricyclics	−3.97 [−13.88, 5.94]	1.87 [−3.02, 6.75]	0.29 [−1.12, 1.69]	−0.45 [−5.03, 4.14]	−0.37 [−1.73, 0.99]	−0.41 [−1.92, 1.10]	0.78 [−5.74, 7.29]	5.34 [−1.19, 11.88]	−0.38 [−5.29, 4.52]
SSRI/SNRIs	−5.65 [−11.91, 0.61]	−0.49 [−3.66, 2.69]	0.26 [−0.64, 1.15]	1.66 [−1.21, 4.54]	0.81 [−0.04, 1.66]	0.81 [−0.14, 1.76]	1.45 [−2.73, 5.63]	−1.17 [−5.39, 3.05]	−3.98 [−6.98, −0.98]*
Benzodiazepines	**−9.39 [−16.42, −2.36]***	−0.40 [−4.03, 3.23]	**−1.42 [−2.42, −0.41]***	1.20 [−2.10, 4.51]	0.45 [−0.53, 1.44]	0.20 [−0.89, 1.29]	3.15 [−1.62, 7.92]	−5.47 [−10.19, −0.75]*	−1.31 [−4.77, 2.16]
Stimulants	2.21 [−12.37, 16.78]	0.61 [−6.56, 7.79]	1.20 [−0.86, 3.25]	3.02 [−3.70, 9.75]	0.69 [−1.31, 2.69]	0.63 [−1.59, 2.84]	0.97 [−8.58, 10.52]	4.81 [−4.82, 14.44]	−6.84 [−13.99, 0.30]
Cannabis	5.26 [−4.43, 14.96]	1.95 [−2.83, 6.73]	−0.03 [−1.41, 1.34]	−2.71 [−7.19, 1.77]	−0.77 [−2.10, 0.56]	−1.17 [−2.63, 0.30]	−4.06 [−10.41, 2.29]	1.17 [−5.29, 7.64]	−1.13 [−5.94, 3.68]
Skeletal/muscle relaxants	−2.62 [−11.07, 5.84]	−3.79 [−7.93, 0.34]	0.17 [−1.02, 1.37]	−0.40 [−4.24, 3.44]	0.42 [−0.72, 1.56]	−0.30 [−1.58, 0.99]	2.22 [−3.33, 7.77]	−3.41 [−9.10, 2.29]	−3.36 [−7.44, 0.71]
Antispasmodics	−2.42 [−8.53, 3.69]	1.69 [−1.36, 4.74]	−0.38 [−1.25, 0.49]	−1.10 [−3.92, 1.72]	−0.34 [−1.17, 0.50]	**−0.94 [−1.86, −0.02]***	−1.59 [−5.64, 2.46]	−3.26 [−7.36, 0.83]	−0.20 [−3.20, 2.79]
Sedatives	−1.74 [−13.56, 10.08]	0.17 [−5.66, 5.99]	−0.62 [−2.29, 1.04]	2.75 [−2.70, 8.19]	1.43 [−0.18, 3.04]	1.67 [−0.11, 3.45]	−4.98 [−12.69, 2.74]	1.58 [−6.25, 9.42]	1.15 [−4.70, 6.99]
Number of high risk medication categories	−1.75 [−3.47, −0.04]*	−0.35 [−1.21, 0.52]	−0.18 [−0.43, 0.06]	0.13 [−0.67, 0.93]	0.09 [−0.14, 0.33]	−0.07 [−0.33, 0.20]	0.27 [−0.88, 1.42]	−1.12 [−2.27, 0.04]	−1.33 [−2.15, −0.50]*†

Note. SSRI = serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; PASAT = Paced Auditory Serial Addition Test; CVLT = California Verbal Learning Test; DKEFS = Delis-Kaplan Executive Function System; PROMIS = Patient Reported Outcomes Measurement Information System.
* Unadjusted p value significant $p < .05$; † false discovery rate-adjusted $q < .15$. Each cell represents an independent, adjusted, linear regression model. All models adjust for age, sex, education (≥college vs. <college), and injury classification (i.e., tetraplegia vs. paraplegia). Bolding indicates significant findings following backward selection models.

considered in the context of the use of other medications, opioid analgesics were only medication category that was independently associated with executive function and subjective cognitive complaints. This finding would be consistent with other studies that have a similar inverse relationship (van Steenbergen et al., 2017).

In addition, there was some evidence to suggest that benzodiazepine use may be associated with slower processing speed, poorer working memory, and worse executive function, but not with other cognitive domains (i.e., attention, delayed free recall memory, or subjective cognitive complaints). When considered in the context of other medication classes, benzodiazepines were the only medication category to be independently associated with processing speed and working memory. These findings would be consistent with published findings that suggest that benzodiazepines impact cognitive control (an aspect of processing speed, attention and executive functioning; Leicht et al., 2013).

Furthermore, there was some evidence to suggest that anticonvulsants may be related to worse learning. This finding would be consistent with other studies that have reported a similar relationship (at least for the older class anticonvulsants, that are represented in this category; Sabers et al., 1995). This is also true for the significant relationship between antispasmodics and long delay free recall memory, where previous literature has found a similar relationship (Ancelin et al., 2006; Campbell et al., 2009; Pasina et al., 2013). In addition, as expected, we did not see significant relationships with antidepressants. This is not surprising given that the sample was not depressed as a group.

Contrary to our hypotheses, we were surprised to find that cannabis, skeletal muscle relaxants, and sedatives were not related to cognitive performance, nor to subjective reports of cognitive function. With regard to cannabis, while the general literature has repeatedly found a relationship for cannabis to have an acute effect on cognition there is less evidence to support long-term cognitive effects (for review see Broyd et al., 2016). With regard to sedatives, there is strong evidence for acute effects (for review see Stranks & Crowe, 2014) and evidence, although more controversial, for long-term effects (for review see Stewart, 2005). With regard to skeletal muscle relaxants, there is some evidence to support a negative relationship between skeletal muscle relaxant use and cognition for some medications (i.e., cyclobenzaprine), but not others (tolperisone; Caron et al., 2020). Thus, it is possible that by combining these different subcategories in the current analysis (e.g., centrally acting skeletal muscle relaxants vs. other types of skeletal muscle relaxants), we may have washed out potential effects. We also did not see a significant relationship between simulant medication use and cognition. Given the small sample size for this group (n = 7 individuals), future exploration of this relationship is warranted.

Finally, findings suggest that the number of medication categories a person with SCI may be negatively related to cognitive performance, but only for processing speed, and subjective cognitive function. This finding, if replicated, would add to a small body of literature that has found other negative outcomes (although all these studies focused on physical problems, rather than cognition) related to polypharmacy in persons with SCI—this includes drug-related problems (e.g., adverse events/side effects, intoxication due to drug interactions; Hand et al., 2018; Kitzman et al., 2017; Patel et al., 2017) and constipation (Harari et al., 1997). Other studies in SCI have reported high rates of polypharmacy among people with SCI (although the definition of polypharmacy varies study by study; Atkins et al., 2014; Goodman et al., 2014; Guilcher et al., 2018; Hatch et al., 2018; Kitzman et al., 2017; Patel et al., 2017; Rouleau & Guertin, 2011) In this study, the average number of medication classes that an individual was on was 2.1, which is comparable to other published findings (which report that 68% of people with SCI, out of sample of 7,399 people with SCI, were on two or more high-risk medications; Kitzman et al., 2017).

In addition to these findings, it is important to acknowledge several study limitations. First, findings for an association between medication use and cognition should be considered preliminary, as they were not maintained after a correction for multiple comparisons were employed. Future studies are warranted to replicate the findings between different medication classes and objective cognitive performance. In addition, this study relied on participant self-report of both prescription and non-prescription medication use, as well as for comorbid conditions. Future work should consider using self-report data in conjunction with medical records, pharmacy records, and/or medical claims databases to confirm medication use and medical history. Furthermore, this sample tended to be highly educated, which does/does not represent the typical SCI population. In addition, reports for common comorbidities are low and reflect the reliance on self-report data, but it also suggests that this sample is higher functioning than the typical SCI population. The cognitive test scores (which were generally within normal limits) would support the latter premise. We also did not include any symptom validity measures, and thus it is possible symptom reporting may be exaggerated/inaccurate in this study. Furthermore, we examined classes of drugs, rather than individual drugs; it is possible that some drugs within a class have differential effects on cognition. It is also possible that we would have found more relationships if we had examined subgroups (e.g., those with clinically significant levels of depression or anxiety, those with comorbid traumatic brain injuries) rather than examining at the group level as done in this study. It is also possible that the secondary conditions that prompted taking various medications (e.g., depression, chronic pain) play an important role in cognitive performance; examination of the role of these conditions and symptoms is warranted. Further research confirming the relationships found in this study is needed. We also did not collect information about medication dosing or length of time using medication; future work should consider further examination of these factors and either association with cognitive performance.

In sum, there appears to at least some preliminary support for a negative relationship between medication use, specifically benzodiazepine and opioid analgesic use, and cognitive performance in people with SCI. Future work in more heterogeneous samples is needed to confirm these findings that highlight the need for more research in these areas.

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