Spinal Cord Series and Cases (2021)7:50
https://doi.org/10.1038/s41394-021-00413-6

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ARTICLE

The treatment of neurogenic lower urinary tract dysfunction in persons with spinal cord injury: An open label, pilot study of anticholinergic agent vs. mirabegron to evaluate cognitive impact and efficacy

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Received: 9 March 2021 / Revised: 19 May 2021 / Accepted: 20 May 2021

Abstract

Study design Pre–post intervention.

Objectives

1. To test whether replacement of oral anticholinergic (AC) agents with mirabegron for neurogenic lower urinary tract dysfunction (NLUTD) yields improved cognitive function in older persons with spinal cord injury (SCI).
2. To test whether mirabegron is safe and as efficacious as AC.

Setting USA.

Methods *Pilot study*: Twenty older (>60 y/o) persons with SCI taking chronic (>6 months) AC medication for NLUTD were enrolled. All participants were first studied on AC at baseline then switched to mirabegron for 6 months. Primary outcomes were cognitive tests of (1) executive function (TEXAS, SDMT); (2) attention (SCWT); and (3) memory (SLUMS and WMS-IV Story A/B). Secondary outcomes assessed efficacy and safety including Neurogenic Bladder Symptom Score (NBSS), bladder diary, neurogenic bowel dysfunction (NBD) survey, heart rate (HR), electrocardiogram (EKG), and mean arterial pressure (MAP).

Results When switching from AC to mirabegron for NLUTD, older persons with SCI exhibited statistically significant improvements in immediate Story A recall ($p = 0.01$), delayed story A and B recall ($p = 0.01$, 0.004), and in TEXAS ($p = 0.04$). Three subscores within NBSS significantly improved ($p = 0.001$) and the frequency of incontinence decreased ($p = 0.03$) on mirabegron. NBD, HR, MAP, and EKGs were unchanged.

Conclusions Older persons with SCI on AC for NLUTD demonstrated improved short-term and delayed memory (WMS-IV Story A/B) as well as executive function (TEXAS) when switched to mirabegron. Efficacy of mirabegron for NLUTD symptoms was superior to AC with no adverse effects on bowel or cardiovascular function.

Sponsorship Claude D. Pepper Older Americans Independence Center.

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Published online: 10 June 2021

Introduction

Approximately 285,000 persons in the United States are living with a spinal cord injury (SCI) with an incidence of 17,500 persons annually [1]. Post-SCI loss of supraspinal bladder innervation impairs urine storage and evacuation resulting in 'neurogenic lower urinary tract dysfunction' (NLUTD). As a result of NLUTD, up to 81% of persons with SCI experience urinary incontinence, urinary frequency, and frequent urinary tract infections (UTIs) [2, 3]. Treatment of NLUTD often requires lifelong treatment [2, 3]. Anticholinergic (AC) agents are currently the first-line pharmacological therapy for NLUTD with evidence of poor detrusor compliance and/or neurogenic detrusor overactivity. AC agents competitively but non-selectively, inhibit binding of the neurotransmitter, acetylcholine to all (M1–M5) muscarinic cholinergic receptors. The blocking of M3 receptors located at neuromuscular junctions in the human bladder detrusor muscle relaxes the detrusor smooth muscle and increases bladder capacity; however, due to the wide distribution of muscarinic cholinergic receptor subtypes (M1–M5) in the central nervous system and body, AC agents can have undesirable side effects including xerostomia, dry eye syndrome, blurred vision, constipation, as well as delirium or cognitive impairment/memory loss, especially in older persons.

Older SCI persons are particularly susceptible to the adverse cognitive effects of AC medications due to: (1) reduced cholinergic activity related to decreased acetylcholine synthesis and/or a decrease in acetylcholine receptors [4]; (2) increased blood–brain barrier permeability [5]; and (3) lower *p*-glycoprotein activity, which is an efflux central nervous system transporter [6]. Overall, these age-related changes increase the probability that AC medications will cause cognitive dysfunction. Furthermore, in 2003, Perry et al. [7] reported that AC use is associated with increased Alzheimer's disease-related pathology. In the first prospective cohort study, Gray et al. demonstrated an association between higher cumulative AC medication use and increased risk for dementia [8]. In 2016, Risacher et al. [9] showed that AC medication use is associated with increased brain atrophy, reduced brain glucose metabolism, and decline in both general cognition and specific cognitive domains (memory and executive function) in older adults. According to the World Health Organization, AC agent use is one of the few modifiable risk factors that has been identified for dementia [10] and therefore recommend minimizing the use of AC agents. The American Geriatrics Society Beers Criteria advise providers against using AC agents in the older [11]. Due to the foregoing, AC agents appear to be best avoided in older persons if at all possible [12].

In 2012, a new Beta-3 adrenoreceptor agonist (Mirabegron) was FDA-approved for the treatment of overactive bladder which is functionally similar to neurogenic detrusor overactivity from NLUTD but is not neurogenic in etiology [13]. Mirabegron stimulates B_3-adrenoreceptors and thus affects detrusor smooth muscle relaxation, decreases afferent signaling from the bladder, and increases bladder capacity. Therefore, mirabegron is not only expected to be effective in overactive bladder, consistent with FDA approval but also NLUT dysfunction associated with poor detrusor compliance and neurogenic detrusor overactivity [14]. Given this agent's different mechanism of action, it is unsurprising that the adverse effect profile is different than AC-associated adverse effects, e.g., no cognitive impairment. Preliminary trials ($N = 15$) of off-label use of mirabegron in persons with SCI and NLUTD suggest that it is as effective and tolerable as AC agents for incontinence, increasing bladder capacity, decreasing voiding frequency, and detrusor compliance [15–17], thus, mirabegron appears to hold promise for NLUTD in patients with SCI.

Based on the foregoing, we hypothesized that cognition in older persons with SCI taking AC agents for NLUTD would improve when switched to mirabegron. Three main domains of cognitive function were assessed by neuropsychological measures: (1) memory, the processes of encoding information, information storage, and retrieval; 2) attention, the ability to maintain awareness of specific stimuli, sensations, or thoughts while disregarding others; and (3) executive function, the ability to critically assess situations, manipulate abstract information to solve complex problems, and direct behavior towards a goal. Secondarily, we hypothesized that mirabegron efficacy in treating NLUTD symptoms would be comparable or better than AC. Finally, to assess safety, cardiovascular parameters (i.e. heart rate (HR), mean arterial pressure, and electrical conduction) were monitored.

Materials and methods

43 persons were screened using the inclusion and exclusion criteria in Table 1.

After screening, 20 were enrolled (19 male, 1 female). Demographics are reported in Table 2. The most frequent cause of exclusion was cardiac dysrhythmias (Fig. 1). After visit 1, the AC agent was discontinued and replaced with 25 mg mirabegron.

In a pre–post study design, all (primary and secondary) outcome measures were initially collected while on AC for baseline/control data (i.e.; 0 months). Participants were then switched to mirabegron. Outcome measures were repeated at various intervals while on 6 months of mirabegron treatment per the visit schedule outlined in Table 3.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	1. Both genders with spinal cord injury being treated for neurogenic bladder and age >60 years
	2. Taking a minimum regimen of 3 months with AC (e.g., solefenacin, oxybutynin, trospium) for bladder control
	3. All ethnic groups
	4. Veterans
	5. Labs: "normal" clinical labs for CBC, CMP, and UA within past 6 months or repeat at screening if none. For example, GFR ≥ 30 mL/min, liver enzymes (AST < 2 × upper limits of normal, ALT < 2 × upper limits of normal, alkaline phosphatase < 2 × upper limit of normal), normal electrolytes, urinalysis stable and asymptomatic for UTI
Exclusion criteria	1. Diagnosis of dementia or cognitive impairment from another condition such as traumatic brain injury, Alzheimers, Lewy body dementia, or vascular dementia
	2. End-stage renal disease (GFR < 30) or bladder obstruction
	3. Poorly controlled blood pressure (systolic BP > 180, diastolic BP > 110 mmHg)
	4. Renal function—exclude if serum creatinine >2× normal range
	5. Liver function—exclude if >2× normal liver enzyme levels
	6. History of, or currently active treatment for cardiac dysrhythmias, including atrial fibrillation
	7. Concomitant treatment with another AC agent for mood or pain.
	8. Active/unstable conditions: inflammatory, thyroid, autoimmune, gastrointestinal (GI), hematologic, or neoplastic disorders.
	9. Subject is considered unsuitable for the study in the opinion of the investigator for any other reason

Table 2 Participant demographics: age, AC agent with daily dose, and years on AC agent.

Participant ID	Age (years)	AC agent (daily dose)	Length of time (years) on AC agent
1	65	Oxybutynin (20 mg)	11
2	63	Oxybutynin (15 mg)	4
3	66	Oxybutynin SA (20 mg)	4
4	63	Oxybutynin SA (20 mg)	4
5	66	Oxybutynin SA (10 mg)	18
6	66	Tolterodine SA (2 mg)	10
7	81	Oxybutynin SA (10 mg)	2
8	68	Oxybutynin SA (20 mg)	23
9	75	Oxybutynin (15 mg)	12
10	63	Trospium (40 mg)	6
11	62	Solefenacin (5 mg)	3
12	84	Trospium (40 mg)	3
13	73	Trospium (40 mg)	6
14	78	Oxybutynin (10 mg)	1
15	73	Trospium (20 mg)	3
16	77	Oxybutynin SA (20 mg)	14
17	63	Trospium (40 mg)	4
18	63	Solefenacin (10 mg)	6
19	64	Trospium (40 mg)	1
20	70	Oxybutynin SA (30 mg)	6
Mean	69.2 yrs		7.1 yrs

Primary outcome measures

Cognitive tests

Measured a range of cognitive functions including memory, executive function, and attention. Tests included: (1) Weschler Memory Scale IV [18] (WMS-IV); (2) Saint Louis University Mental Status Exam (SLUMS) [19]; (3) The Telephone Executive Assessment Scale [20] (TEXAS); (4) Symbol Digit Modality Test [21] (SDMT); and (5) Stroop Color-Word Test [22] (SCWT) (Table 4 for descriptions). These tests were conducted at 0 months on AC and after 6 months of mirabegron therapy.

All cognitive assessments were administered by a clinical research nurse, who was trained and approved for testing by a geriatric neuropsychologist. Cognitive assessments were only conducted twice within a 6-month spanning interval to avoid confounding (i.e.; learning) effects of repeated testing. Some aspects of executive function tests that require a motor function that is compromised in SCI persons (i.e. hand function), therefore, the cognitive assessments chosen were those that did not

require upper arm motor function, consistent with past SCI cognition studies [23].

Secondary outcome measures

Efficacy

To ensure comparable efficacy to AC, bladder function assessments (i.e. bladder diary (BD) and Neurogenic Bladder Symptom Score (NBSS)) were performed monthly.

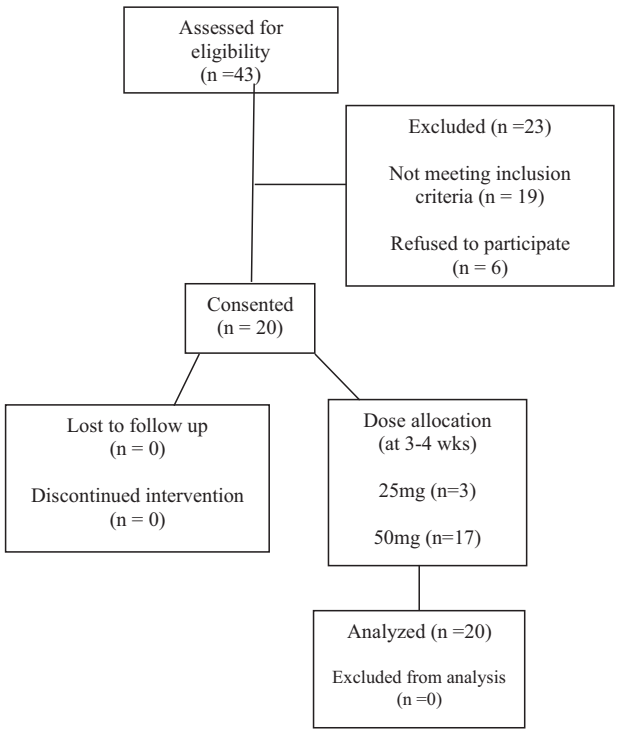

Fig. 1 Consort chart. Consort diagram showing the flow of participants through each stage of the trial.

BD was specifically developed for this study. Measured the frequency of bladder evacuation (BE)/24 h, frequency of incontinence (FI)/24 h, number of *symptomatic* urinary tract infections (SUTI)/month, urine output volume (UOP) (ml) per void, and average urine output (ml) per 24 h (UOP24).

Neurogenic Bladder Symptom Score

This validated quality of life (QOL) measure for urological problems in SCI specifically assesses symptoms and bladder-related consequences for NLUTD in SCI through 24 questions, divided into 4 subsections of Total incontinence (TI), total storage and voiding (TSV), total consequences (TC) and urinary specific QOL [24, 25]. These questions elucidate the frequency and quantity of urine leakage, the impact on health and everyday activities, the frequency and severity of UTIs, and the frequency of bladder and kidney stones. The total score can range from 0 (minimal symptoms) to 74 (maximum symptoms).

Safety

As mirabegron is a beta-3 agonist, to assess potential off-target beta-adrenergic effects, HR and mean arterial blood pressure (MAP) were recorded monthly. All MAP and HR measurements were conducted at the same time of day (within the hour) for each patient at Visit 1, 4, and 7. One BP and one HR recording were taken each visit. A standard 12 lead electrocardiogram with a rhythm strip was obtained every 3 months to assess changes in HR, rhythm, or conduction and was interpreted by a cardiologist. In addition, some studies in elderly persons on mirabegron have reported constipation could worsen due to beta-3 bowel receptors [26]. The validated neurogenic bowel dysfunction (NBD) survey [27] has two sections, "severity of dysfunction" (0–6 = Very Minor, 7–9 = Minor,

Table 3 Outline of procedures conducted each monthly visit.

Visit #	V1 (clinic)	V2 (phone)	V3 (phone)	V4 (clinic)	V5 (phone)	V6 (phone)	V7 (clinic)
Visit description	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
#Weeks on treatment	Week 0	Up to 7 d prior to Week 4	Week 5–8	Up to 7 d prior to Week 12	Week 13–16	Week 17–20	Week 21–26
Consent	X						
Vital signs (HR, BP)	X			X			X
Safety labs (CBC, CMP, UA)	X			X			X
Electrocardiogram (ECG)	X			X			X
Urinary assessment (NBSS + bladder diary)	X	X	X	X	X	X	X
Bowel assessment (NBD)	X	X	X	X	X	X	X
Cognitive assessments (WMS-IV, TEXAS, SLUMS, SDMT, SCWT)	X						X
Dispense 25 mg mirabegron dose	X						
Titrate mirabegron up to 50 mg (if applicable)		X					

Table 4 Battery of cognitive assessments utilized to assess memory, executive function, and attention.

	Description
Memory	
WMS-IV (logical memory subset)	Story A and B: Both stories are unique. Story A is shorter (2–3 sentences) and is repeated once. Story B is a paragraph. After each story is orally presented, immediate recall is tested by the question, "Tell me everything you can remember about this story. Start at the beginning". Meanwhile, delayed recall of story A and B is tested after a 20–30 min delay. Each correct detail is awarded with one score point.
SLUMS	Consists of 11 questions that test orientation, memory, attention, and executive function, with items such as animal naming, digit span, figure recognition, clock drawing, and size differentiation. Maximum score is 30 points and cut-offs for dementia or mild cognitive impairment (MCI) are based on education level[a].
Executive function	
TEXAS	Comprised of five items from the Exit Interview (EXIT 25) that can be administered by telephone, i.e., "Number-Letter Task", "Word Fluency", "Memory/Distraction Task", "Serial Order Reversal Task", and "Anomalous Sentence Repetition" items. Total TEXAS scores range from 0 to 10, with higher scores corresponding to greater impairment.
SDMT	Using a reference key, the examinee has 90 s to pair specific Arabic numbers 1–9 with the associated geometric figure. Points are given for correct answers (110 maximum). A score is obtained by subtracting the number of errors from the number of items completed within the given timeframe. The SDMT oral version was used in this assessment battery.
Attention	
SCWT	The examinee responds to word and color stimuli as a measure of selective attention—for example, the word red may be printed in the congruent color (red), an incongruent color (e.g., blue), or a neutral color (e.g., black). The time (in seconds) is recorded to complete Page 1—reading aloud color words printed in black, Page 2—reading aloud the color word congruent with the ink color and Page 3—reading aloud the ink color incongruent with the color word. The response to interference of competing stimuli (the Stroop effect) is assessed on page 3.

[a]Since each participant served as their own control, we did not collect education level information.

10–13 = Moderate, 14+ = Severe) and "general satisfaction" (0 = perfect and 10= total dissatisfaction). The NBD survey was collected monthly.

After baseline data were collected, participants were started on mirabegron 25 mg daily. After 3 weeks, participants were called and queried for any significant adverse changes in BD measures as listed above. If there were any adverse changes in BD measures (e.g. increased FI), the dose was increased to 50 mg daily. After this optimal dosing was determined, participants remained on that mirabegron dose for the remainder of the study (~5 months) (Table 1).

Statistical analysis

Primary outcomes

Raw mean scores of each cognitive test (WMS-IV story A and B, SLUMS, SDMT, SWCT, and TEXAS) were calculated then analyzed via a paired samples *t*-test to evaluate for significant differences in scores at V1 vs. V7.

Secondary outcomes

BD measures including frequency of BE/24 h, FI/24 h, number of SUTI/month, UOP (ml) per void, and average urine output (ml) per 24 h (UOP24) and NBSS data were analyzed via repeated-measures ANOVA. Each of the first three measures on sheet NBBS were analyzed separately with a mixed model ANOVA followed by Dunnett's test to compare each visit with V1. Ordinal measures were analyzed with one-way repeated ordinal regression using the CLMM package in R. Before analysis, each ordinal measure was recoded with rank numbers ranging from low to high (the recoded measures are indicated by a lower case *r*). NBD interval measures were analyzed with a mixed model ANOVA. For all analyses, the statistical threshold for significance was set at $p < 0.05$.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The VA-affiliate, University of Texas Health San Antonio Institutional Review Board (#20180376H) approved the study.

Results

Cognitive tests (primary outcome measures)

Memory

SLUMS scores showed no significant difference ($p = 0.39$) between V1 and V7 (Fig. 2). Similarly, WMS-IV Story A first immediate recall and Story B immediate recall did not show significant differences ($p = 0.09$ and $p = 0.22$, respectively) between V1 and V7. On the other hand, the second immediate Story A recall significantly differed between V1 and V7 ($p = 0.01$). Delayed recall of Story A and B scores also were significantly improved on AC vs mirabegron ($p = 0.01$ and 0.004, respectively) between V1 and V7, respectively.

Executive function

SDMT "correct" scores showed no significant difference ($p = 0.12$) between V1 and V7. SDMT "incorrect" scores

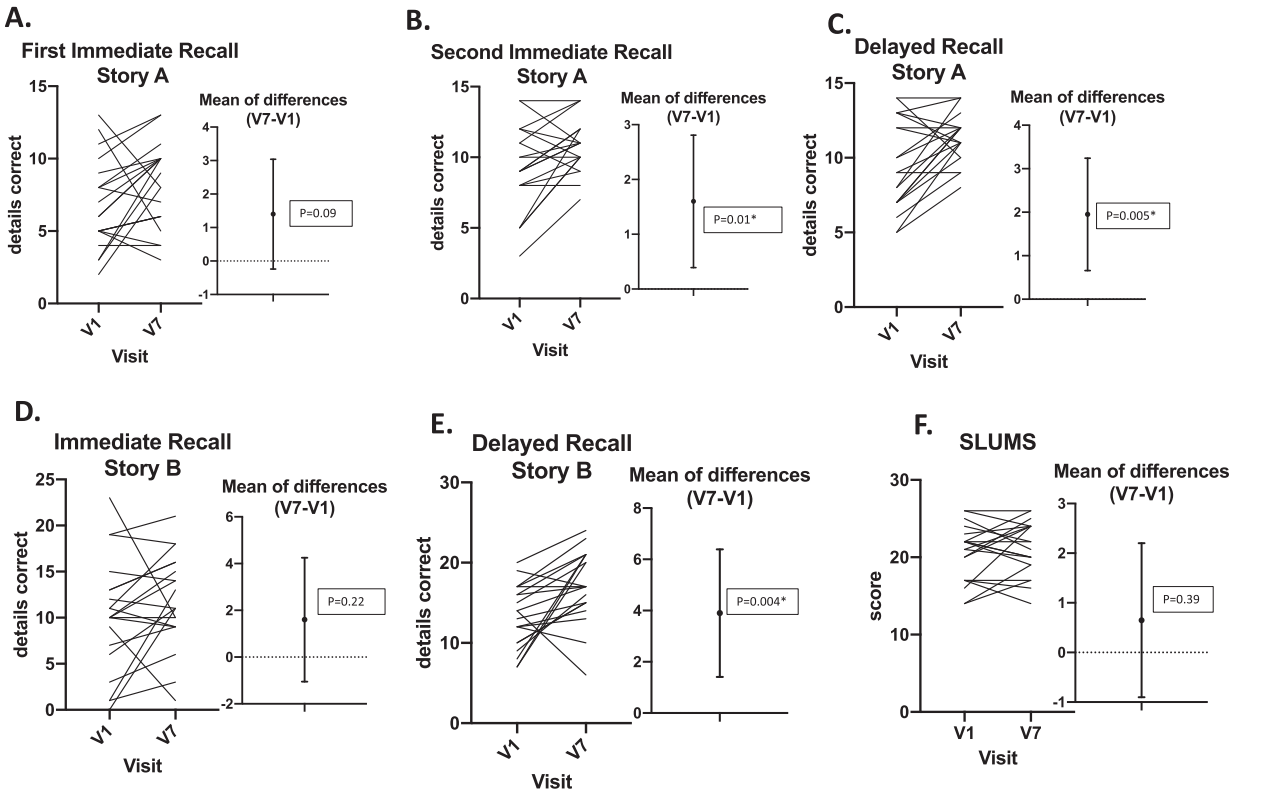

Fig. 2 Scores from memory assessments of Weschler Memory Scale IV (WMSIV). Logical Memory subset (**A**–**E**) and Saint Louis University Mental Status (SLUMS) (**F**) at V1 vs. V7. **A** Story A first immediate; **B** Story A second immediate, **C** Story A delayed recall, **D** Story B immediate recall, **E** Story B delayed recall and **F** SLUMS. In each panel, the right-hand figure shows the mean difference between visits and its 95% confidence interval.

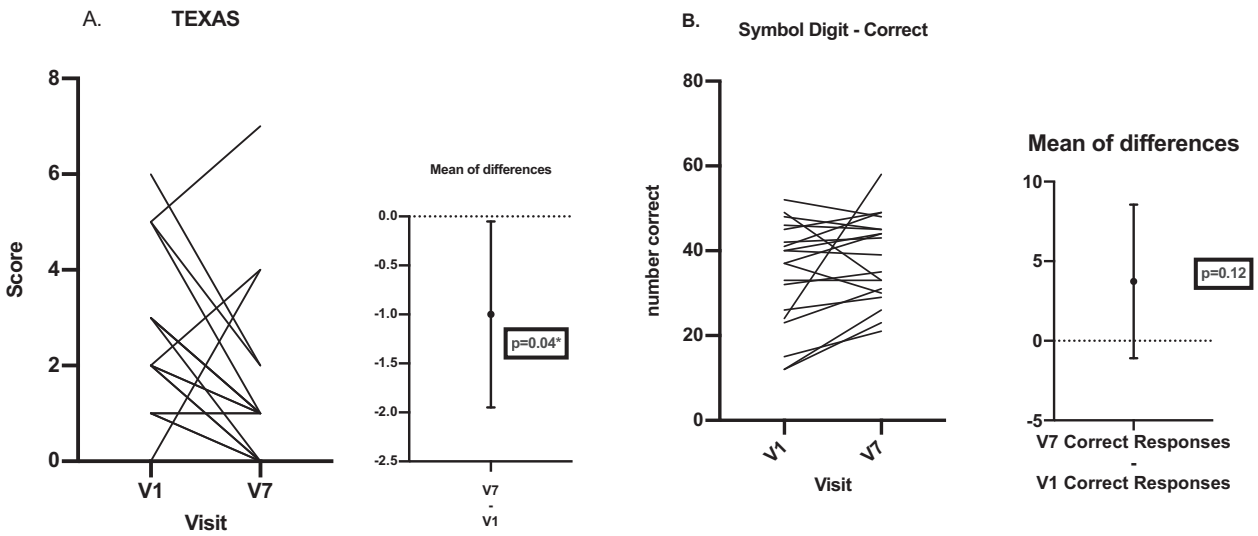

Fig. 3 Executive function test scores on AC (V1) vs. mirabegron (V7). A Telephone Executive Assessment Scale (TEXAS) and **B** Symbot Digit Modailty Test (SDMT).

also showed no significant difference ($p = 0.16$) between V1 and V7 (data not shown). On the other hand, TEXAS scores significantly improved ($p = 0.04$) from V1 to V7 (Fig. 3).

Attention

SCWT scores were not significantly different between V1 and V7 on any page (pages 1–3) ($p = 0.21, 0.18, 0.14$, respectively).

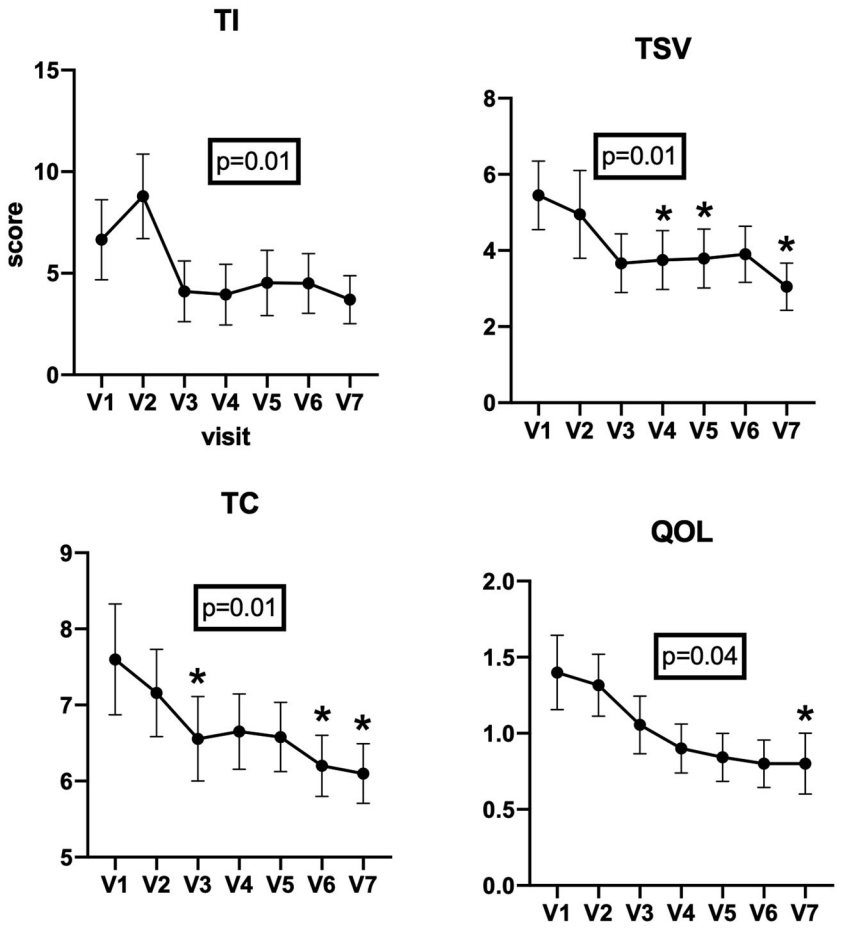

Fig. 4 Neurogenic bladder symptom score results. Neurogenic Bladder Symptom Score (NBSS) results with 4 subsections of Total Incontinence (TI), Total consequences (TC), Total storage and voiding (TSV), and urinary specific quality of life (QOL) which all statistically improved after switching from AC to mirabegron.

Bladder and bowel function

Bladder diary

Within the BD data, the FI was the only measure that showed a significant effect of visit ($p = 0.02$) and a statistically significant decrease between V1 (mean rank number 1.50) and V7 (mean rank number 1.15) ($p = 0.03$). All other measures (BE, SUTI, UOP, UOP24) did not differ statistically over the 6 months.

NBSS scores

TI, TSV, and TC showed a statistically significant overall effect of visit ($p = 0.01$, 0.01, 0.01), with TSV and TC being significantly lower at V7 than V1 and at V4 and V3, respectively. NBSS QOL domain (0 = pleased, 4 = unhappy) showed a significant effect of visit ($p = 0.03$) and a significant difference between V1 and V7 ($p = 0.04$) (Fig. 4).

NBD

Neither "severity" ($p = 0.13$) or "general satisfaction" ($p = 0.28$) showed statistically significant effects of visit.

Cardiovascular parameters

HR and MAP did not significantly differ between visit (i.e. V1 (baseline/AC agent) vs. V4 (mirabegron) and V7 (mirabegron)) (HR: $p = 0.31$; MAP: $p = 0.22$) (Table 5). EKG rhythms were unchanged in all participants from V1 to V7. Post hoc analysis of HR and MAP data showed neither a statistically significant effect of dose (25 mg vs. 50 mg) ($p = 0.59$), visit (V1, V4, V7) ($p = 0.42$) nor a significant dose × visit interaction ($p = 0.57$).

Discussion

Given that persons with SCI have an increased risk of cognitive impairment, about 13 times higher than age-matched healthy controls [28, 29]; and the knowledge that AC agents carry a higher risk of dementia [9], identifying AC treatment alternatives in persons with SCI and NLUTD is desirable. This is the first study to examine the cognitive impact of removing AC agents and substituting mirabegron in persons with SCI and the comparative efficacy (NLUTD symptoms) and potential side effects on bowel and cardiovascular functions. It is

Table 5 Heart rate (HR) and mean arterial pressure (MAP) values (mean ± SD) at visit 1 (0 months), visit 4 (3 months), and Visit 7 (6 months).

	Visit 1 Anticholinergic	Visit 4 Mirabegron	Visit 7 Mirabegron	*F* (DFn, DFd)	*p* value
HR (beats per min)	73.85 (13.82)	76.55 (13.74)	71.75 (12.9)	$F(0.4002, 5.803) = 0.67$	0.31
MAP (mmHg) ($n = 20$)	87.32 (9.79)	84 (7.99)	89.3 (10.19)	$F(1.561,22.63) = 1.62$	0.22
25 mg ($n = 3$)[a]	92.89 (9.48)	84.22 (11.79)	88.89 (2.17)		
50 mg ($n = 17$)[a]	86.33 (9.78)	83.93 (7.90)	89.37 (11.07)		

No significant differences in HR or MAP while on AC vs. mirabegron.

[a]No significant main or interaction effects of MAP involving dose and visit.

noteworthy that documented detrimental effects of AC agents on cognition led the American Urological Association to update its guidelines in 2015 to include mirabegron as an alternative first-line agent for overactive bladder treatment. This study was conducted in hopes to demonstrate a lower side effect profile of mirabegron (compared to AC) with similar efficacy in persons with SCI with NLUTD. We found cognitive benefits in the realms of memory and executive function with mirabegron compared to AC treatment for NLUTD while improving efficacy and maintaining safety.

Memory

The Weschler Memory Scale-IV has been used as the main outcome measure in studies of cognitive decline in older persons *without* SCI [9]. We chose this measure to evaluate cognition in our older population *with* SCI. We used the Weschler Memory Scale-Revised Logical Memory Immediate Recall whose subsection of Story A and B did not require motor function. Interestingly, there was a significant improvement in the Wechsler logical memory stories on immediate and delayed recall. While the stories are strongly related to memory function, they also have an executive function component due to their structure with a beginning, middle, and end, which a respondent can utilize to organize their responses.

The second memory exam we used was SLUMS which just like the Mini-Mental Status Exam (MMSE) predicts mortality and institutionalization for male patients screened as positive for dementia [30]. SLUMS is suggested to be more sensitive than MMSE [30]. We found no significant change in the SLUMS scores which is not unexpected as the SLUMS is a screening assessment for cognitive impairment that has a limited number of memory items as well as other items related to general cognition. It is not conceptualized as a memory test, but more as a brief general cognitive screen, which even over a year re-test interval following medication or cognitive intervention, often do not show significant change [31].

Executive function

The TEXAS [20] tests executive function and is comprised of five items from the Exit Interview (EXIT25) [32] that can be administered by telephone. Four of those appear on the Quick EXIT and EXIT15. Switching from AC to mirabegron significantly improved the TEXAS score. This could be explained as these test items were extracted from the EXIT25 as the strongest items correlated with the total EXIT score representing an executive function [20, 32].

The SDMT assesses divided attention, visual scanning, tracking, and motor speed using a symbol/digit substitution task. It is sensitive to change in neurocognitive status, thus making it useful for evaluating interventions with good test–retest ($r = 0.76$) and alternate forms ($r = 0.82$, $r = 0.84$) reliability [33]. It also distinguishes between individuals with depression and those with organic dementia. There was no statistically significant change in SDMT scores after switching from AC to mirabegron. The lack of change in the SDMT could be explained by interpreting it as a complex multifactorial task that involves many components of executive function that include visual selective attention, visual scanning, processing speed, and even memory. Finally, A total raw score likely does not reflect independent contributions of these different components which could have improved.

Attention/psychomotor speed

SCWT assesses the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. There was no significant change in SCWT after switching from AC to mirabegron. This finding could be related to the selective visual attention requirement and cognitive flexibility that both could result in poor performance due to cognitive slowing seen in normal aging. Furthermore, deficiencies in reading aloud may also be influencing decreased Stroop performance related to low education, language problems (articulation and verbal fluency), bilingualism, and even respiratory and mood issues.

All participants were English speaking however education level was not assessed which is a limitation.

Efficacy and safety outcomes

NLUTD symptoms

NLUTD function measured by NBSS (median score is 19 out of a possible 74 with higher scores relating to worse symptoms) and BD both demonstrated no worsening of bladder function with improvement in many subscores (TC, TSV, TI, FI) over time. TC subscore improvement means there was overall less frequent and severe UTIs, less pain with voiding, fewer kidney/bladder stones, and bladder medication efficacy. TSV subscore improvement suggests mirabegron had an overall positive impact on the frequency of urgency, nocturia, the interval between emptying, stream, straining, and post-void fullness. TI and FI score improvements show mirabegron collectively improved frequency of daytime and nighttime incontinence, degree of saturation and number of pads used daily, oral fluid restriction, skin problems, and limitation of activities. Notably, urinary specific QOL on NBSS improved which is significant as the recovery of bladder function is one of the highest priorities of persons with SCI [34]. This subjective data suggests that mirabegron is either as effective or more effective than AC in the treatment of NLUTD. However, objective data from urodynamic studies (filling and voiding pressures) should be collected in future studies to most objectively compare the efficacy of AC vs. mirabegron.

Safety

The NBD assessment did not show any change in bowel function. The most concerning potential adverse effect was a change in HR or MAP; however, no significant changes were found. EKG monitoring also showed no change in rhythm. Thus, the safety (NBD, HR, and MAP) and efficacy (NBSS and BD) data gathered in this study revealed no major adverse effects caused by the switch from AC to mirabegron.

Limitations

Practice effects on all cognitive tests have been observed so a follow-up larger and longer study (1–2 years) may be needed to show significant findings consistent with these results that can then be interpreted as reliable cognitive indicators of significant change related to mirabegron. In addition, It should be noted that both the SDMT and SCWT tests have one common characteristic that involves a participant using controlled eye movements that are integrated with frontal eye fields and visual pathways that connect to the occipital lobe as part of the participant's task in order to respond. Ocular-motor integration is an active neurocognitive area of study relating to visual perception and executive function but was not specifically examined in this study. Finally, the small sample size of this pilot study could also explain some non-statistically significant findings.

Conclusion

Substituting mirabegron for AC agents in older persons with SCI provides some cognitive benefit in the realms of executive function and memory as evidenced by significant improvement in scores of TEXAS and of the WMS-IV logical memory recall stories A and B, respectively. In addition, some therapeutic benefit in subjective NLUTD symptomatology (e.g. FI, TSV, TC) was also found. These benefits come without adverse impacts on bowel function or cardiovascular changes (HR, MAP, and EKG). Given the intrinsic impaired cognitive function of persons with SCI compared to age-matched controls, risk of dementia with chronic AC use, and the intrinsic risk of dementia in the older (>60 y/o) population, use of mirabegron should be considered prior to AC for NLUTD treatment in the older population with SCI to preserve cognition.

Data archiving

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements This material is the result of work supported with resources and the use of facilities at the Audie L. Murphy Veteran's Affairs Hospital in San Antonio, TX.

Funding Funding is provided by Claude D. Pepper Older Americans Idependence Center.

Compliance with ethical standards

Conflict of interest While SK (author) does acknowledge conflict of interest with the manufacturer of Mirabegron (Astellas), he did not have access to data from the study that could have potentially created bias in results.

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