Fesoterodine ameliorates autonomic dysreflexia while improving lower urinary tract function and urinary incontinence-related quality of life in individuals with spinal cord injury

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Fesoterodine ameliorates AD following SCI

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ABSTRACT

The aim of this prospective phase IIa, open-label exploratory, pre-post study was to determine the efficacy of fesoterodine (i.e., 12-week treatment period) to ameliorate autonomic dysreflexia (AD) in individuals with chronic SCI (>1-year post-injury) at or above the sixth thoracic spinal segment, with confirmed history of AD and neurogenic detrusor overactivity (NDO). Twelve participants (4 females, 8 males; median age 42 years) completed this study and underwent urodynamics, 24-hour ambulatory-blood-pressure-monitoring (ABPM), and urinary incontinence-related quality of life (QoL) measures at baseline and on-treatment. The Montreal Cognitive Assessment (MoCA) and Neurogenic Bowel Dysfunction (NBD) score were used to monitor cognitive and bowel function, respectively. Compared to baseline, fesoterodine improved lower urinary tract (LUT) function, i.e., increased cystometric capacity (205 vs 475mL, p = 0.002) and decreased maximum detrusor pressure (44 vs 12cmH_2O, p = 0.009). NDO was eliminated in seven (58%) participants. Severity of AD events during urodynamics (40 vs 27mmHg, p = 0.08) and 24-hour ABPM (59 vs. 36mmHg, p = 0.05) were both reduced, yielding a large effect size (r = -0.58). AD Frequency (14 vs. 3, p = 0.004) during 24-hour ABPM was significantly reduced. Urinary incontinence-related QoL improved (68 vs. 82, p = 0.02), however, cognitive (p = 0.2) and bowel function (p = 0.4) did not change significantly. In conclusion, fesoterodine reduces the magnitude and frequency of AD, while improving LUT function and urinary incontinence-related QoL in individuals with chronic SCI without negatively affecting cognitive or bowel function.

Neurogenic detrusor overactivity (NDO) and autonomic dysreflexia (AD) combine to place a tremendous burden on health and quality of life (QoL) in individuals living with a spinal cord injury (SCI). We have previously shown that the presence of NDO and the neurological level of injury (NLI) are independent risk factors for developing AD during urodynamic studies (UDS).[1] The higher the NLI above the sixth thoracic spinal cord segment (T6), the higher the odds of experiencing AD. Since AD can lead to potentially life-threatening complications, such as stroke, myocardial infarction, or even death, urologists should take precautions when conducting UDS in this population.[2] Furthermore, we have provided evidence that onabotulinumtoxinA, a second-line treatment option, ameliorates AD while effectively improving lower urinary tract (LUT) function and urinary incontinence-related QoL.[3] However, whether antimuscarinics (i.e., first-line treatment option) have the capacity to ameliorate AD in this cohort has not yet been investigated. Thus, our aim was to determine whether fesoterodine is effective in reducing the incidence and severity of AD episodes during UDS and in daily life in individuals with chronic (>1-year post-injury) SCI ≥ T6.[4]

MATERIAL AND METHODS

This prospective phase IIa, open-label exploratory, non-blinded, non-randomised, single-centre pre-post study was approved by the University of British Columbia Clinical Research Ethics Board (H15-02364), Vancouver Coastal Health Research Institute (V15-02364) and Health Canada (205857). Furthermore, this study was registered at clinicaltrials.gov (identifier NCT02676154). A study protocol, adhering to the standard protocol items: recommendations for interventional trials and consolidated standards of reporting trials statements has been previously published.[4]

After screening twenty individuals with chronic SCI ≥ T6, fifteen individuals with confirmed history of AD and NDO provided written informed consent according to the Helsinki II declaration

and underwent a battery of baseline assessments (Supplemental Figure 1). The NLI and completeness (i.e. American Spinal Injury Association impairment scale [AIS] grade) of SCI were classified according to the International Standards for Neurological Classification of SCI.[5] All UDS (Aquarius TT, Laborie Model 94-R03-BT, Montreal, Quebec, Canada) were performed in accordance with the International Continence Society.[6] Concurrent to UDS, we continuously recorded beat-by-beat blood pressure via finger photoplethysmography (Finometer PRO, Finapres Medical Systems, Amsterdam, Netherlands), corrected to brachial pressure (CARESCAPE V100, GE Healthcare, Milwaukee, WI, USA), and one-lead electrocardiogram (eML 132; ADInstruments, Colorado Springs, CO, USA) for heart rate in order to detect AD.[1, 7]

After confirmation of AD during baseline UDS, frequency and severity of AD in daily life were recorded using 24-hour ambulatory-blood-pressure-monitoring (ABPM, Meditech Card(X)plore device, Meditech, Budapest, Hungary).[8] All participants completed validated, standardized questionnaires to subjectively monitor urinary incontinence-related QoL (I-QoL),[9] AD health-related QoL (AD-HR-QoL)[8], bowel function (neurogenic bowel dysfunction [NBD] Score)[10] and cognitive function (Montreal cognitive assessment [MoCA][11]), respectively. Ten to twelve weeks following the start of treatment, objective and subjective measures were repeated to assess on-treatment efficacy.

The aim of this study was to assess the effect of fesoterodine (i.e., 12-week treatment period; on-treatment compared to baseline) in reducing the severity of AD (i.e., maximum increase in systolic blood pressure [SBP]) during UDS, as well as severity and frequency of AD occurring in daily living as detected during the 24-hour ABPM. The two primary outcome measures were number of participants who experienced a decrease in severity of AD during UDS and 24-hour ABPM. Secondary outcome measures included: the improvement in UDS parameters (e.g., cystometric capacity and detrusor pressure); number of participants who experienced a decrease in the frequency of AD in daily life (i.e., during 24-hour ABPM); number of participants who experienced a reduction in self-reported AD severity and frequency (i.e., AD-HR-QoL); an

improvement of self-reported urinary incontinence-related QoL (i.e., I-QoL); an improvement in bowel (i.e., NBD Score) and cognitive function (i.e., MoCA, total score ≥26 considered as unimpaired cognitive function).

Following baseline assessments, eligible individuals received a 4-week supply of 4mg daily doses of fesoterodine. During the treatment period, individuals returned to the study centre (i.e., at the latest 2 days before their supply ran out). During these visits, participants were assessed for dose efficacy. In consultation with the investigator, individuals had a choice to either increase the dose of the study drug to 8mg or maintain the same dose (4mg). Participants who elected to increase their dose to 8mg per day had the option to return to 4mg at any time. However, participants only had the option to increase their dose once, meaning that no further increase in dose was permitted following a dose reduction. Study drug compliance was monitored using a diary to identify missed doses. Participants were asked to indicate the days where doses were missed. Non-adherence was considered when an individual failed to take fesoterodine consecutively (>5 days) or intermittent (>50% of all days within one cycle). Lastly, we recorded any adverse drug reactions (ADRs) over the course of the 12-week treatment period.

Statistical analysis was performed using R Statistical Software Version 4.0.5 for Mac Os. Considering the limited size of our cohort, non-parametric statistics (i.e. Wilcoxon signed-rank test) were used to compare within participants (i.e. baseline vs. on-treatment assessment). Data are presented as median with lower and upper quartiles (Q1; Q3); and minimum and maximum for age and time post-injury). Furthermore, effect size expressed as Pearson correlation coefficient, i.e. Pearson's (r) was calculated as Z statistics divided by square root of total number of pairs (N) in accordance with Rosenthal:[12]

$$r = \frac{Z}{\sqrt{N}}$$

Pearson's r can vary in magnitude from −1 to 1, with −1 indicating a perfect negative linear relation, 1 indicating a perfect positive linear relation, and 0 indicating no linear relation between

two variables (effect sizes: small, r = 0.1 – 0.29 or -0.1 – (-0.29); medium, r = 0.3 – 0.49 or -0.3 – (-0.49); large, r ≥ 0.5 or -0.5).

RESULTS

In total, 12 individuals [4 females, 8 males; mean age 42 years (36; 50, 29 – 52) and mean time post-injury 19 years (12; 22, 7 – 39)] completed the study and were included for analysis (Supplemental Table 1). The majority had cervical (n=8), motor-complete (AIS A/B = 10) SCI.

Regarding our primary outcome, 10 (83%) and 9 (75%) participants experienced a decrease in severity of AD during UDS and during daily life, respectively. Further, fesoterodine ameliorated objectively measured AD, i.e., smaller increase (Δ) in systolic blood pressure (SBP) during on-treatment UDS compared to baseline [Figure 1A, 40 mmHg (24; 44) vs. 27 mmHg (14; 33), p = 0.08, Z = -2, r = -0.58] and severity of AD (ΔSBP) until cystometric capacity from the baseline UDS was reached during on-treatment UDS [Figure 1B, 40 mmHg (24; 44) vs. 4.5 mmHg (0; 10.5), p = 0.002, Z = -3, r = -0.87]. Furthermore, the severity [Figure 1C, 59 mmHg (48; 69) vs. 36 mmHg (28; 56), p = 0.04, Z = -2, r = -0.58] and frequency [Figure 1D, 14 (5; 28) vs. 3 (2; 12), p = 0.004, Z = -3, r = -0.87], of AD during daily life measured by 24-h-ABPM were significantly reduced on-treatment. Subjectively, fesoterodine reduced the frequency [Figure 1E, 8.5 (6; 11) vs. 7 (4.2; 9.2), p = 0.2, Z = -1, r = -0.29] and severity [Figure 1F, 4.5 (2.8; 8.5) vs. 3 (2; 6.5), p = 0.2, Z = -1, r = -0.29] of bladder-related AD symptoms in daily life.

Further, fesoterodine objectively improved LUT function. Cystometric capacity [Figure 1G, 205 mL (144; 300) vs. 475 mL (331; 555), p = 0.002, Z = 3, r = 0.87] increased significantly. Volume at first NDO [Figure 1H, 125 mL (65; 178) vs. 215 mL (165; 290), p = 0.1, Z = 2, r = 0.58] also increased but did not yield statistical significance. However, the effect of volume increase was large, considering that only five individuals (-58%) had NDO while being on-treatment.

Further, fesoterodine significantly decreased maximum detrusor pressure during bladder filling [Figure 1J, 44 cmH_2O (24; 56) vs. 12 cmH_2O (6; 26), p = 0.009, Z = -3, r = -0.87].

In addition, urinary incontinence-related QoL, assessed using the I-QoL questionnaire, was significantly improved overall, i.e., *in total* [Figure 2A, 68 (55; 80) vs. 82 (77; 90), p = 0.02, Z = 2, r = 0.58] as well as in sub-categories *Psychological Impact* [Figure 2B, 84 (54; 95) vs. 92 (83; 100), p = 0.006, Z = 3, r = 0.87] and *Social Embarrassment* [Figure 2C, 50 (39; 80) vs. 78 (55; 90), p = 0.04, Z = 2, r = 0.58]. In addition, sub-category *Avoidance* [Figure 2D, 68 (50; 84) vs. 82 (77; 88), p = 0.1, Z = 2, r = 0.58] was improved by a large magnitude but did not yield statistical significance. Further, we observed no changes in bowel function, i.e. NBD total score [Figure 2E, 9.0 (6.0; 12.5) vs. 8.5 (6.0; 13.2), p = 0.7, Z = 0, r = 0; and NBD general satisfaction [7 (5.8; 8) vs. 8 (5.8; 8), p = 0.4, Z = 1, r = 0.29], without any negative effect on cognitive function [Figure 2F, MoCA, 29.0 (25.8; 29.2) vs. 29.0 (28.0; 30), p = 0.2, Z = 1, r = 0.29].

All 12 participants adhered to the study protocol including the intake of fesoterodine. At the end of the treatment phase, daily dosage distribution among participants was even, i.e. 4mg (n = 6) or 8mg (n = 6). Overall, we recorded 26 ADRs in 10 participants (Table 1), i.e. related (n = 23) or possibly related (n = 3), which were all grade 1 (n = 21) or 2 (n = 5).

DISCUSSION

The majority of our cohort experienced a decrease in severity of AD during UDS and in daily life without any significant deterioration of cognitive or bowel function. Further, in line with our previous study, highlighting an efficacious second-line treatment (i.e. intradetrusor onabotulinumtoxinA injections),[3] we observed significant improvements of LUT function and urinary incontinence-related QoL in individuals being on-treatment with fesoterodine.

Yonguc et al.[13] reported significant improvements in overactive bladder (OAB) symptoms in older patients with Parkinson's disease (i.e., mean age 66 years) on-treatment with fesoterodine 4mg without affecting cognitive function. In another study, DuBeau et al.[14] showed that fesoterodine (i.e., 12-week treatment 4mg to 8mg per day) not only led to significantly greater improvements in urgency urinary incontinence episodes per 24 hours and QoL in the elderly (i.e., mean age 75 years) but also did not negatively affect cognitive function (i.e., mini-mental state examination) compared to placebo. Fesoterodine is the only antimuscarinic agent with a 'fit for the aged' (FORTA) classification B (i.e. beneficial, "*drugs with proven or obvious efficacy in older people, but limited extent of effect or safety concerns*").[15] Wagg et al.[16] also highlighted the clinical efficacy and safety of OAB treatment (i.e., 12 weeks with 4mg to 8mg per day) in patients aged ≥65 years. Although our cohort was younger than the aforementioned studies, i.e., <65 years of age, our findings confirm the previously established safety profile of fesoterodine (i.e., only grade 1 and 2 ADRs). Further, we did not observe a dosage-dependent frequency or distribution of ADRs.

Given the vulnerability of our cohort with respect to cognitive impairment,[17] these findings are important, as fesoterodine (as well as other antimuscarinics) is not only a first-line treatment option but for some individuals is the only option covered by their healthcare insurance. For example, Canadian provincial healthcare coverage often does not include second-line treatments, such as onabutulinumtoxinA, thus presenting significant socioeconomic burden. Given its design, our study has several limitations, such as a lack of blinding, placebo group, and follow-up beyond 3 months as well as the limited cohort size, which should be considered when interpreting our findings.

CONCLUSIONS

In conclusion, our findings highlight that fesoterodine, a first-line treatment option for NDO, ameliorates AD during UDS and in daily life in individuals with SCI ≥ T6. Fesoterodine also improves LUT function and urinary incontinence-related QoL without negatively affecting bowel and cognitive function. Considering the increased risk of cardiovascular disease in this cohort,[18] these findings are crucial as sudden increases in systolic blood pressure can result in life-threatening consequences, jeopardizing the well-being and QoL of individuals with SCI.

Author contributions

Andrei V. Krassioukov had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design:

Matthias Walter, Andrea Ramirez, Daniel Rapoport, Alex Kavanagh, Andrei V. Krassioukov

Acquisition of data:

Matthias Walter, Andrea Ramirez, Amanda H.X. Lee, Thomas E. Nightingale, Daniel Rapoport, Alex Kavanagh, Andrei V. Krassioukov

Analysis and interpretation of data:

Matthias Walter, Andrea Ramirez, Amanda H.X. Lee, Thomas E. Nightingale, Daniel Rapoport, Alex Kavanagh, Andrei V. Krassioukov

Statistical analysis:

Matthias Walter

Drafting of the manuscript:

Matthias Walter

Critical revision of the manuscript for important intellectual content:

Andrea Ramirez, Amanda H.X. Lee, Thomas E. Nightingale, Daniel Rapoport, Alex Kavanagh, Andrei V. Krassioukov

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Administrative, technical, or material support:

Teresa Lim, Grace Coo, Ivy Allard, Colleen McLean, Tammy Wilder.

Supervision:

Andrei V. Krassioukov

Conflict of interest

Pfizer Canada was not the sponsor of this investigator-initiated study. However, Pfizer Canada supported this study financially and provided the study drug in-kind. Pfizer Canada had no role in the trial design, data collection, interpretation of the data, preparation of the manuscript, final approval of the manuscript or decision to publish this manuscript. However, Pfizer Canada was given the opportunity to review the content of the current manuscript version as per agreement, i.e. prior to submission.

REFERENCES

1. Walter, M., Knupfer, S.C., Cragg, J.J., Leitner, L., Schneider, M.P., Mehnert, U., Krassioukov, A.V., Schubert, M., Curt, A. and Kessler, T.M. (2018). Prediction of autonomic dysreflexia during urodynamics: a prospective cohort study. BMC medicine 16, 53.

2. Wan, D. and Krassioukov, A.V. (2014). Life-threatening outcomes associated with autonomic dysreflexia: a clinical review. J Spinal Cord Med 37, 2-10.

3. Walter, M., Kran, S.L., Ramirez, A.L., Rapoport, D., Nigro, M.K., Stothers, L., Kavanagh, A. and Krassioukov, A.V. (2020). Intradetrusor OnabotulinumtoxinA Injections Ameliorate Autonomic Dysreflexia while Improving Lower Urinary Tract Function and Urinary Incontinence-Related Quality of Life in Individuals with Cervical and Upper Thoracic Spinal Cord Injury. Journal of neurotrauma.

4. Walter, M., Ramirez, A.L., Lee, A.H., Rapoport, D., Kavanagh, A. and Krassioukov, A.V. (2018). Protocol for a phase II, open-label exploratory study investigating the efficacy of fesoterodine for treatment of adult patients with spinal cord injury suffering from neurogenic detrusor overactivity for amelioration of autonomic dysreflexia. BMJ open 8, e024084.

5. Kirshblum, S.C., Burns, S.P., Biering-Sorensen, F., Donovan, W., Graves, D.E., Jha, A., Johansen, M., Jones, L., Krassioukov, A., Mulcahey, M.J., Schmidt-Read, M. and Waring, W. (2011). International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 34, 535-546.

6. Schafer, W., Abrams, P., Liao, L., Mattiasson, A., Pesce, F., Spangberg, A., Sterling, A.M., Zinner, N.R. and van Kerrebroeck, P. (2002). Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 21, 261-274.

7. Walter, M., Lee, A.H.X., Kavanagh, A., Phillips, A.A. and Krassioukov, A.V. (2018). Epidural Spinal Cord Stimulation Acutely Modulates Lower Urinary Tract and Bowel Function Following Spinal Cord Injury: A Case Report. Frontiers in physiology 9, 1816.

8. Hubli, M., Gee, C.M. and Krassioukov, A.V. (2015). Refined assessment of blood pressure instability after spinal cord injury. American journal of hypertension 28, 173-181.

9. Wagner, T.H., Patrick, D.L., Bavendam, T.G., Martin, M.L. and Buesching, D.P. (1996). Quality of life of persons with urinary incontinence: development of a new measure. Urology 47, 67-71; discussion 71-62.

10. Krogh, K., Christensen, P., Sabroe, S. and Laurberg, S. (2006). Neurogenic bowel dysfunction score. Spinal cord 44, 625-631.

11. Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L. and Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 53, 695-699.

12. Rosenthal, R. (1994). Parametric measures of effect size. In: *The handbook of research synthesis.* Russell Sage Foundation: New York, NY, US, pps. 231-244.

13. Yonguc, T., Sefik, E., Inci, I., Kusbeci, O.Y., Celik, S., Aydın, M.E. and Polat, S. (2020). Randomized, controlled trial of fesoterodine fumarate for overactive bladder in Parkinson's disease. World journal of urology 38, 2013-2019.

14. Dubeau, C.E., Kraus, S.R., Griebling, T.L., Newman, D.K., Wyman, J.F., Johnson, T.M., 2nd, Ouslander, J.G., Sun, F., Gong, J. and Bavendam, T. (2014). Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo controlled trial. The Journal of urology 191, 395-404.

15. Oelke, M., Becher, K., Castro-Diaz, D., Chartier-Kastler, E., Kirby, M., Wagg, A. and Wehling, M. (2015). Appropriateness of oral drugs for long-term treatment of lower urinary tract symptoms in older persons: results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014). Age and ageing 44, 745-755.

16. Wagg, A., Arumi, D., Herschorn, S., Angulo Cuesta, J., Haab, F., Ntanios, F., Carlsson, M. and Oelke, M. (2017). A pooled analysis of the efficacy of fesoterodine for the treatment of overactive bladder, and the relationship between safety, co-morbidity and polypharmacy in patients aged 65 years or older. Age and ageing 46, 620-626.

17. Sachdeva, R., Gao, F., Chan, C.C.H. and Krassioukov, A.V. (2018). Cognitive function after spinal cord injury: A systematic review. Neurology 91, 611-621.

18. Cragg, J.J., Noonan, V.K., Krassioukov, A. and Borisoff, J. (2013). Cardiovascular disease and spinal cord injury: results from a national population health survey. Neurology 81, 723-728.

FIGURE LEGEND

Figure 1 – Effect of fesoterodine on AD during UDS and in daily life, and on LUT function.

This figure provides an overview of comparisons between on-treatment and baseline assessments. (A) This subplot highlights the severity of AD (i.e. ΔSBP) during UDS (i.e. until cystometric capacity was reached in each UDS, which were different as shown in subplot G). (B)* highlights the change in severity of AD until cystometric capacity from baseline UDS was reached during on-treatment UDS (i.e. identical volume). (C)* severity of AD in daily life (i.e. during 24-h ABPM). (D)* frequency of AD episodes in daily life, (E) AD symptoms frequency score, (F) AD symptoms severity score, (G)* cystometric capacity, (H) volume at first NDO, and (J)* maximum detrusor pressure during bladder filling (i.e. storage).

ABPM = ambulatory-blood-pressure-monitoring, AD = autonomic dysreflexia, NDO = neurogenic detrusor overactivity, ΔSBP = max. change in systolic blood pressure, UDS = urodynamic studies.

*Data are presented at group level using boxplots (median, upper and lower quartiles, and interquartile range) and individually (dots). * Statistically significant changes (p<0.05)*

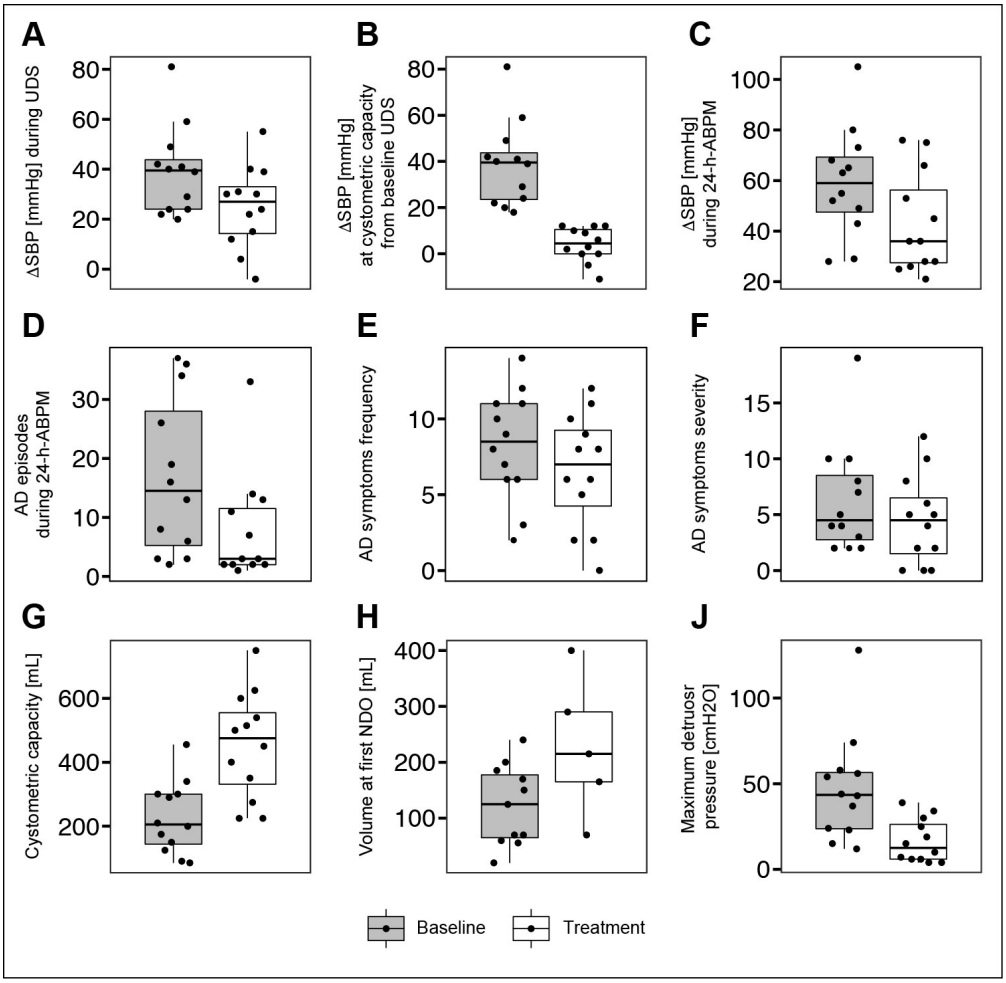

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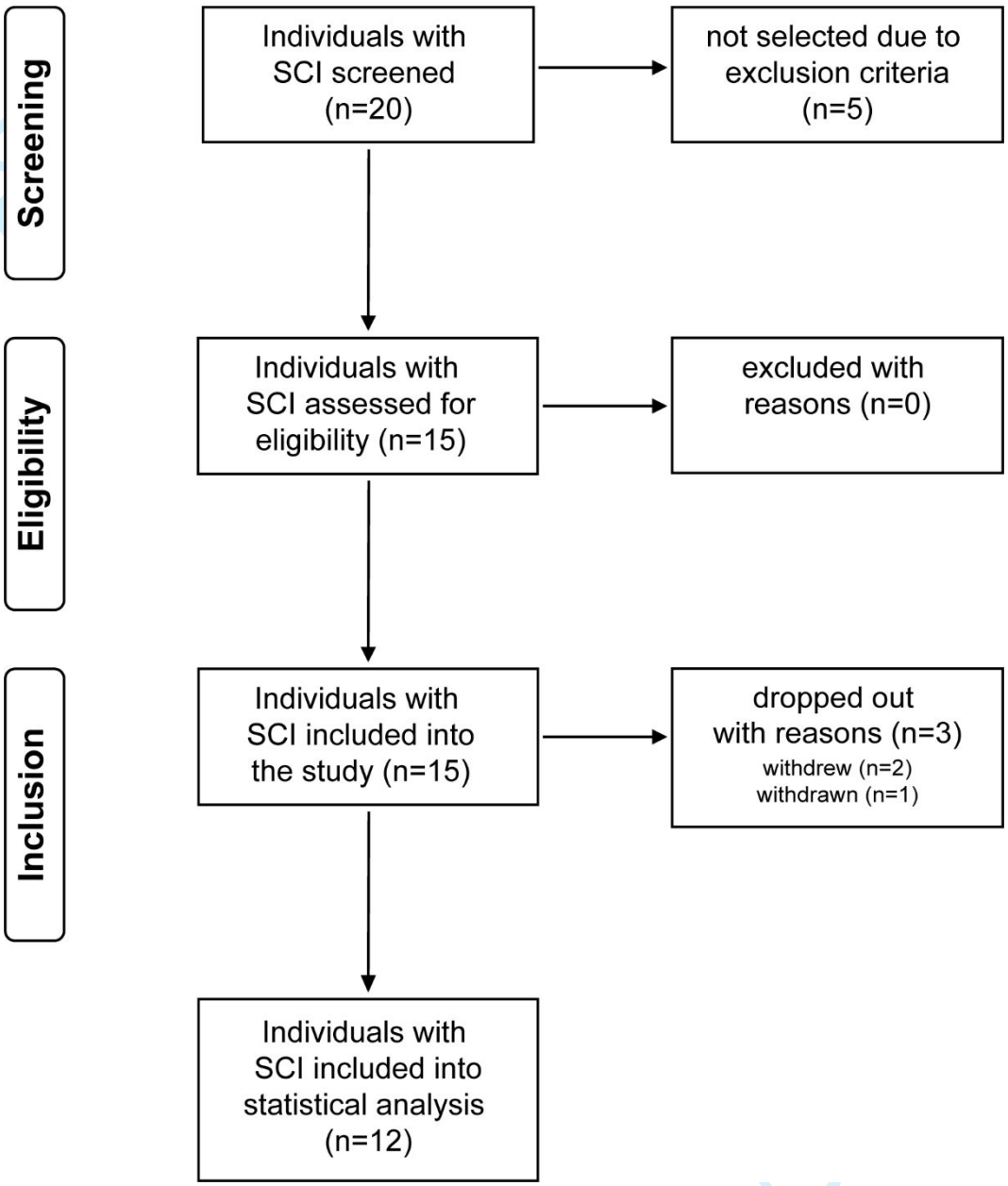
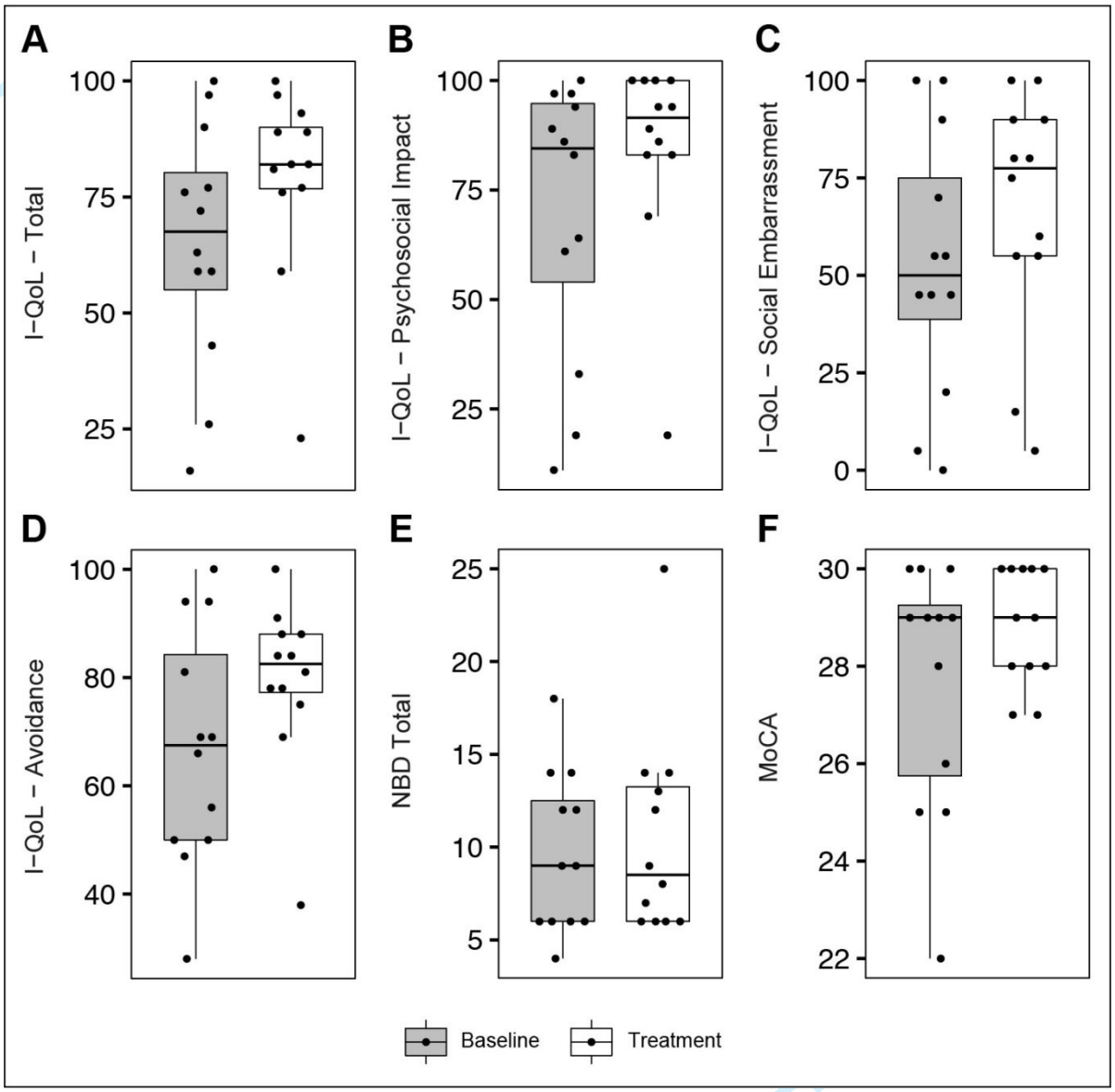
Table 1 – Safety monitoring highlighting the number and distribution of adverse drug reactions

Adverse drug reactions (ADRs)	Overall frequency	ADRs per 4-week cycle and Fesoterodine dosage		
		I (4mg)	II (4 or 8mg)	III (4 or 8mg)
Related*	**23 (88%)**	**15**	**14 (3 / 11)**	**15 (10 / 5)**
Dry mouth	9	7	5 (1 / 4)	5 (3 / 2)
Dry eyes	3	2	1 (0 / 1)	2 (2 / 0)
Fatigue	3	2	3 (1 / 2)	3 (1 / 2)
Increased constipation	2	0	2 (0 / 2)	2 (1 / 1)
Dyspepsia	2	0	2 (0 / 2)	2 (2 / 0)
Increased GGT level	1	1	1 (1 / 0)	1 (1 / 0)
Dry skin	1	1	0	0
Dizziness	1	1	0	0
Somnolence	1	1	0	0
Possibly related	**3 (12%)**	**3**	**2 (0 / 2)**	**2 (1 / 1)**
Decreased libido	1	1	1 (0 / 1)	1 (0 / 1)
Reduced sensation of touch	1	1	0	0
Fecal incontinence	1	1	1 (0 / 1)	1 (1 / 0)

*** Indicating known adverse drug reactions;** GGT = Gamma-glutamyl transferase



Supplemental Figure 1 – Study flow diagram.



Supplementary Figure 2 – Effect of fesoterodine on urinary incontinence-related QoL, bowel and cognitive function: Comparison between on-treatment and baseline assessments for urinary incontinence related QoL, i.e., I-QoL (A)* *Total*, with subcategories (B)* *psychosocial impact*, (C)* *social embarrassment*, and (D) *avoidance and limiting behavior* as well as bowel, i.e. (E) *NBD* score and cognitive function, i.e. (F) *MoCA*. *Data are presented at group level using boxplots (median, interquartile range) and individually (dots). * Statistically significant changes (p<0.05)*

Supplemental Table 1 - Participant characteristics

No.	NLI	AIS	Sex	Age [year]	Time post-injury [year]	Cycle I Dosage [mg]	Cycle II Dosage [mg]	Cycle III Dosage [mg]
1	C6	D	Male	31-40	21-25	4	8	8
2	T3	A	Male	51-60	36-40	4	8	8
3	T6	A	Female	41-50	31-35	4	4	4
4	T2	A	Male	21-30	11-15	4	8	8
5	C5	A	Male	21-30	11-15	4	8	8
6	C5	B	Male	31-40	11-15	4	4	8
7	C4	B	Female	31-40	16-20	4	8	8
8	C6	B	Female	31-40	16-20	4	8	4
9	C6	A	Female	41-50	21-25	4	4	4
10	C5	C	Male	51-60	21-25	4	8	4
11	T2	B	Male	41-50	6-10	4	4	4
12	C5	A	Male	51-60	16-20	4	8	4
	Cervical = 8	**A = 6**	**Female = 4**	**Median = 42**	**Median = 19**	**4mg = 12**	**4mg = 4**	**4mg = 6**
	Thoracic = 4	**B = 4**	**Male = 8**	**Q1 = 36**	**Q1 = 12**		**8mg = 8**	**8mg = 6**
		C = 1		**Q3 = 50**	**Q3 = 22**			
		D = 1		**Minimum = 26**	**Minimum = 7**			
				Maximum = 52	**Maximum = 39**			

AIS = American Spinal Injury Association impairment scale, NLI = neurological level of injury, Q1 = lower quartile , Q3 = upper quartile

* For information, such as age and time post injury, that would allow the study participant to be easily identifiable, a range is provided rather than specific numbers (10-year range for age and a 5-year range for time post injury).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	3,4
Methods			
Study design	4	Present key elements of study design early in the paper	3-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3-5, and published open access study protocol
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-5, and published open access study protocol
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-5, and published open access study protocol
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	See published open access study protocol
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5, Fig. 1

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Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5, Tab. 1, Fig. 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	5-6, Tabl. 2, Fig. 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6, Tabl. 2, Fig. 2-3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-6, Tabl. 2, Fig. 2-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6-7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Transparency, Rigor and Reproducibility Summary

The study design and analysis plan were preregistered on February 8, 2016 at clinicaltrials.gov (NCT02676154). The analysis plan was not formally pre-registered. We did not prespecify a sample size as highlighted in our published study protocol paper (Walter M, et al. BMJ Open 2018;8:e024084. doi:10.1136/bmjopen-2018-024084) which adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and CONsolidated Standards Of Reporting Trials (CONSORT) statements.

All subjects were assigned to an intervention group (i.e., fesoterodine). 20 subjects were screened, 15 subjects were eligible and enrolled and primary outcomes were assessed in 12 subjects. Participants were not randomized as there was only was one group (i.e. intervention group). Participant blinding was not possible because of the nature of the therapeutic intervention. All materials required to perform the interventions are widely available from Pfizer Canada, Laborie (Montreal, Quebec, Canada), Finapres Medical Systems (Amsterdam, Netherlands), Healthcare (Milwaukee, WI, USA), Meditech (Budapest, Hungary), R Statistical Software Version (online).

The key inclusion criteria (e.g., primary diagnosis or prognostic factor) are established standards in the field. The primary clinical outcome measure is an established standard in the field (Kirshblum et al.,International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011, 34, 535-546. - Schaefer et al., Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002, 21, 261-274. - Hubli et al., Refined assessment of blood pressure instability after spinal cord injury. American journal of hypertension 2015, 28, 173-181. - Wagner et al., Quality of life of persons with urinary incontinence: development of a new measure. Urology 1996, 47, 67-71; discussion 71-62. - Krogh et al., Neurogenic bowel dysfunction score. Spinal cord 2006, 44, 625-631; Nasreddine, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005, 53, 695-699. - Rosenthal. Parametric measures of effect size. In: The handbook of research synthesis. Russell Sage Foundation 1994: New York, NY, US, pps. 231-244.)

Key inclusion criteria and clinical outcomes were assessed by investigators with professional qualifications and specific training as physicians. The statistical tests used were based on the assumptions of non-normal distribution, i.e. non-parametric tests, such as Wilcoxon signed-rank test were conducted with respect to the small sample size. There were no missing data. Effect sizes (expressed as Pearson correlation coefficient, i.e. Pearson's (r)) have been reported in the abstract for primary outcome(s) and main text for all outcomes.

Methods that do not require correction for multiple comparisons were used. No replication or external validation studies have been performed. De-identified data and analytic code have not been deposited but are available upon request. A preprint is freely available (https://www.medrxiv.org/content/10.1101/2022.07.14.22277625v1). The manuscript is not open access at the present time.