

# ACADEMY OF SPINAL CORD INJURY PROFESSIONALS

## DOSE EFFECT OF DROXIDOPA TO NORMALIZE SEATED SYSTOLIC BLOOD PRESSURE IN CHRONIC SPINAL CORD INJURY

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### INTRODUCTION

Interruption of sympathetic cardiovascular autonomic regulation following spinal cord injury (SCI) is associated with hypotension and orthostatic hypotension (OH), particularly in individuals with high cord lesions [1]. Droxidopa is a norepinephrine precursor that has been shown to increase standing blood pressure (BP) and reduce symptoms of orthostatic intolerance in individuals with symptomatic neurogenic OH. [2-4]. We recently reported preliminary evidence of an average increase in seated BP in individuals with SCI following oral administration of 400 mg of droxidopa; however, this dose was effective in only 5 of the 10 subjects tested and the BP effect waned over a 4-hour observation. [5].

**The purpose of this investigation was to identify the droxidopa dose that reliably increases seated systolic blood pressure (SBP) into the normal range (111-130 mmHg) in hypotensive individuals with SCI.**

### METHODS

- During the screening visit, brachial BP was monitored and recorded at 1-minute intervals over a 10-minute seated and a 10-minute supine observation using a standard BP cuff.
- Hypotensive participants with SCI were enrolled into the open-label, dose escalation phase.
- Participants were administered oral droxidopa beginning at 100mg, which was increased by 100mg on subsequent visits until average seated SBP was 110-130 mmHg or if the maximum dose of 800 mg was reached without adequate SBP response
- Five brachial BP readings were recorded, using a standard BP cuff, every 30-minutes, for 4 hours, after administration of droxidopa.

### REFERENCES

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2. Kaufmann, H., et al., Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. *Neurology*, 2014. 83(4): p. 328-35.
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4. Kaufmann, H., et al., Norepinephrine precursor therapy in neurogenic orthostatic hypotension. *Circulation*, 2003. 108(6): p. 724-8.
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ID	No.	Sex	Age (years)	LOI	AIS	DOI (year)	Height (inches)	Weight (kg)	BMI	BL-SBP	Avg Post-SBP	Effective Dose (mg)
DROXI_001	1	M	45	C5-6	A	21	65	72.57	22.0	79.83	102.27	200
DROXI_003	2	M	38	C7	B	13	66	81.82	24.5	92.33	116.03	200
DROXI_004	3	M	52	C5-6	A	36	64	58.82	22.3	58.33	96.57	700
DROXI_005	4	M	56	C4	C	8	68	63.00	21.3	84.00	109.99	400
DROXI_006	5	F	58	C3-C4	A	33	61	45.81	14.8	84.17	122.90	200
DROXI_007	6	M	51	C5-6	B	15	73	90.72	25.5	93.50	112.44	200
DROXI_008	7	M	38	C5-6	A	20	66	79.37	23.8	79.50	105.60	400
DROXI_009	8	M	35	T6	C	8	69	68.03	19.4	102.17	113.60	300
DROXI_010	9	M	24	C4-5	C	7	68	72.75	21.1	98.17	112.94	200
DROXI_011	10	M	37	C7	C	12	71	97.52	27.1	104.17	114.26	200
DROXI_001K	11	F	45	C5-6	A	28	68	52.00	17.6	92.50	92.19	na
DROXI_002K	12	F	42	C5	B	19	62	70.50	27.5	87.17	98.74	200
DROXI_003K	13	F	32	C5	C	7	61	81.00	33.7	99.00	121.17	200
DROXI_004K	14	M	28	C4-5	B	5	70	88.45	27.9	104.50	111.90	100

Table 1: Characteristics of the study participants; LOI: level of injury; AIS: duration of injury; BMI: body mass index; SBP: systolic blood pressure; BL: baseline; Avg Post: average post; mg: milligram

### RESULTS

Of the 46 participants screened, 32 met eligibility criteria, and 16 were enrolled in the trial. Two participants withdrew prior to study start.

- Characteristics of the study participants enrolled in the dose escalation are presented (Table 1), which were mostly males (73%), with cervical (81%), motor complete (AIS A/B: 69%), chronic (15±10 years) injuries.

An effective dose was identified in 13 of the 14 participants who completed testing. Of those with an effective dose:

- 100mg, 300mg, and 700mg: one participant each (8%)
- 200mg: eight participants (62%)
- 400mg two participants (16%)
- One participant (DROXI\_004) did not have a normotensive response to droxidopa at doses ranging from 200 to 700mg.

**Figure 1a.** Average baseline (BL) SBP (90±12 mmHg) was significantly increased to 109±11 mmHg, on average post (Avg Post) administration of the effective dose of droxidopa (p<0.0001).

**Figure 1b.** With the effective dose of droxidopa, the average the change in SBP from BL to Avg Post was 19±11 mmHg (range: 0 to 39 mmHg).

**Figure 2a.** SBP response over the 4-hour observation following administration of the effective dose of droxidopa in the 14 participants. The green area represents our target SBP range; the average percent of post administration SBP recordings within range was 48±25% (range 3 to 81%).

- Observation of SBP ≥ 140 mmHg (red horizontal dashed line) was ~3% overall, which included 31% of SBP recordings in DROXI\_006 and 5% in DROXI\_003k

**Figure 3.** Average SBP response, by effective dose of droxidopa, over the 4-hour observation.

- Seated SBP is within the target range ~90 minutes following administration of droxidopa, which is sustained for ~3 hours (black oval).
- Little evidence of hypertension at 300 minutes is in one participant and unlikely in response to droxidopa.

### SUMMARY & CONCLUSION

- **We identified an effective dose of droxidopa in 93% of participants tested;**
- However, the effective dose varied among this small cohort of participants with SCI.
- **More data are needed to determine:**
  - Effects of the effective dose on orthostatic changes in blood pressure.
  - Long-term safety and effects of droxidopa on blood pressure during routine activities.

Figure 1a

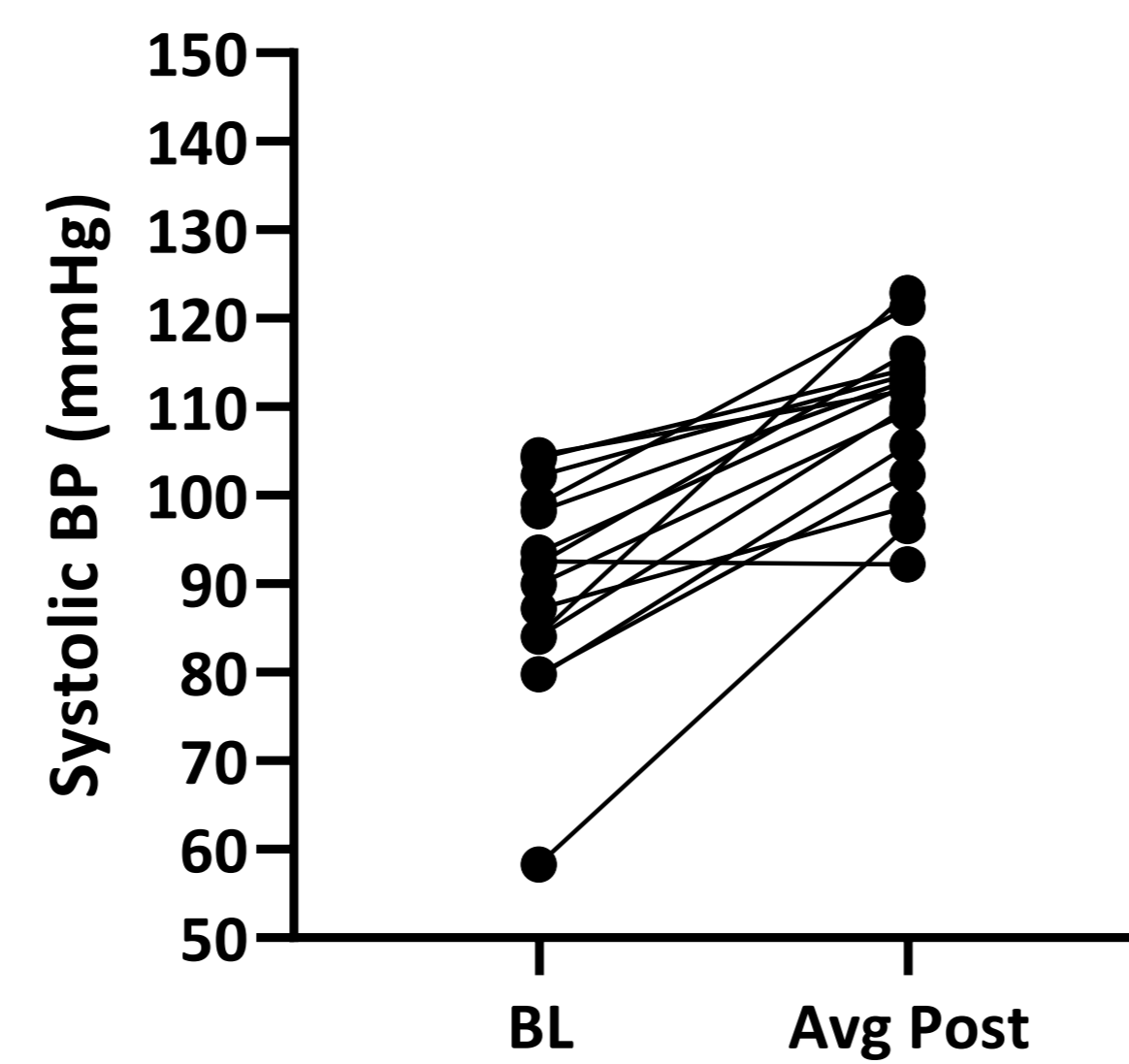


Figure 1b

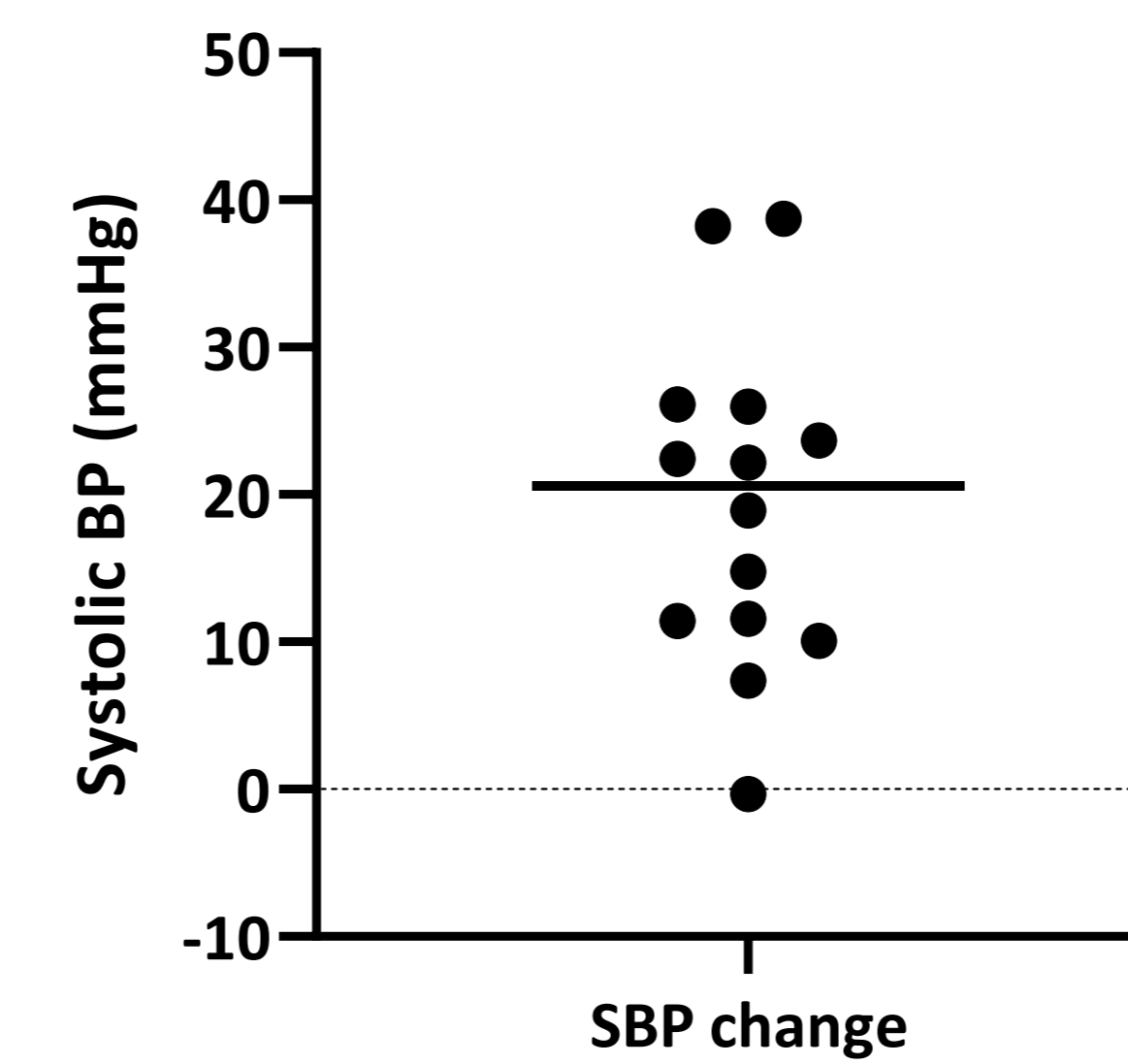


Figure 2a

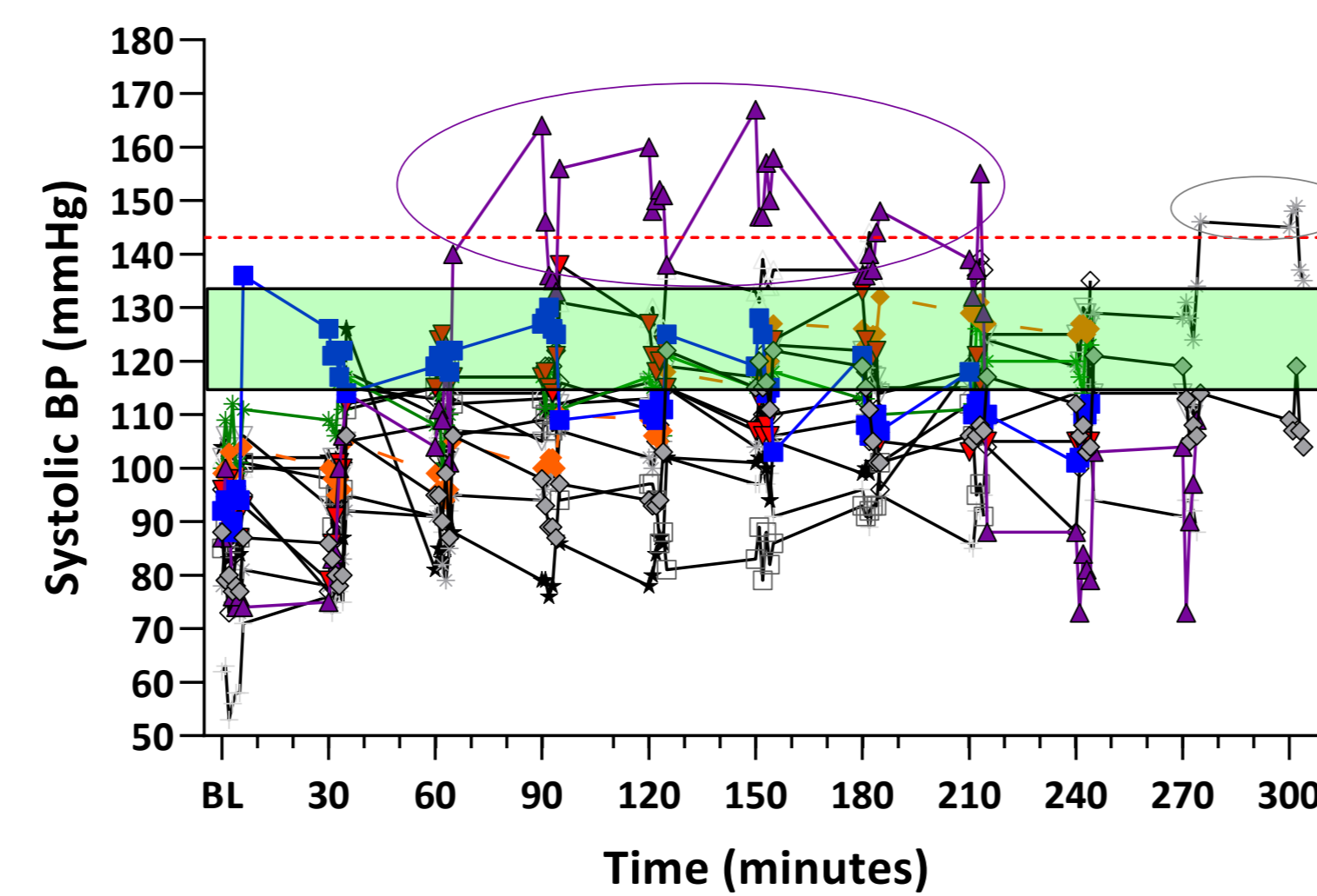


Figure 3

