Have Clinical Trials Under-Evaluated Fampridine's Effect in Multiple Sclerosis?

Tanya King[1], James Close[1], Andrew Blight[1], Lynne Watson[2], Rachael Hunter[2], Gillian Ingram[2], Marguerite Hill[2], Owen Pearson[2], Jeremy Hobart[1]
[1] University of Plymouth* Faculty of Medicine and Dentistry, England, UK
[2] Swansea Bay University Health Board**, Swansea, Wales, UK

Introduction

- Fampridine is licensed for MS. However, its use varies across UK countries.
- Discrepancies exist between:
  - Clinical trial results showing a modest focal benefit on walking.
  - The mode of action implying widespread benefits are possible.
  - Anecdotal patient reports of notable benefits in and outside of walking.
- These discrepancies imply standard clinical trials may have underestimated Fampridine's benefit in breadth, magnitude, and specifics.
- This novel study design, capitalising on Fampridine's quick effect onset, might provide better understandings of Fampridine benefits.

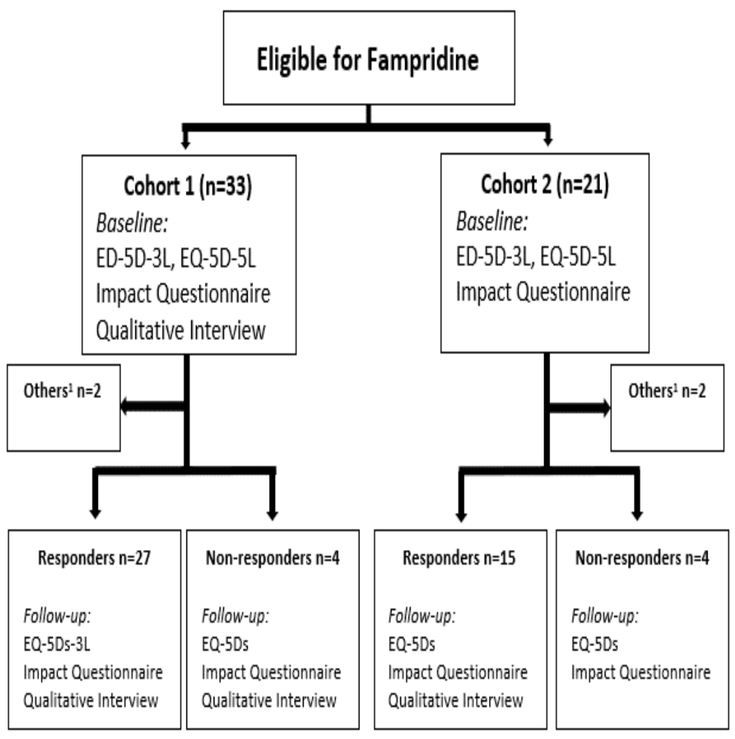
Aims

- To determine:
  - Which aspects of MS are affected by Fampridine, in what way, and to what degree.
  - The mode of action implying widespread benefits are possible.

Method

- Participants were people with MS prescribed Fampridine routinely at two clinical sites; Swansea Bay University Hospital Board (SBUHB) and University Plymouth Hospitals NHS Trust (UPHT).
- The breadth and magnitude of Fampridine's effect was determined using a bespoke 18-domain MS impacts questionnaire.
- Participants completed the EuroQol (EQ-5D) health economic questionnaire.
- The specifics of Fampridine's impact were further explored using qualitative interviews.
- There were two groups:
  - Cohort 1 was the first 33 participants. These were interviewed before and after (≈1 month) starting Fampridine.
  - Cohort 2 was the next 21 people. Of these only the responders were interviewed when their responder status was identified ≈1 after a month of taking Fampridine.
  - All 54 people completed the EQ-5D and the Impact Questionnaire at baseline and follow-up irrespective of responder status (see Fig 1).

Fig 1. Study Design



[1] Discontinued Fampridine before responder assessment due to side effects

Results

Responder Status

- Fig 1 shows, 50 participants (93%) completed treatment, n=4 (7%) discontinued (n=2 from each Cohort) due to side effects before their responder status assessment.
- 42 (84%) were Fampridine responders[2]; n= 27 from Cohort 1, n=15 from Cohort 2.
- 8 (16%) were non responders, n=4 from each Cohort. Table 1 shows their demographics.

Table 1. Sample Demographics

Group	n (%)	Female %	Age (yrs) Mean (SD)	Age (yrs) Range
Total	**50**	**68.0**	**57.1 (9.6)**	**37-75**
Responders[2]	42 (84.0)	66.7	56.9 (8.5)	37-74
Non responders	8 (16.0)	75	58.3 (13.9)	38-75

[2]Responder criteria: **SBUHB ≥20% improvement in Timed 10m Walk Test at 2-4 weeks on Fampridine. *UPHT: anyone who self-funded Fampridine after the 4 week trial (personal cost effectiveness)

Responder Results (n=42)

MS Impact Questionnaire

- Fig 2 shows 95% reported benefits in ≥1 MS impact domain, 76% in 5 domains, 62% in 6 domains, 29% in 10 domains.
- In 10/18 domains, >50% of people reported moderate or significant benefit.

Fig 2 Percent of responders with domains benefited

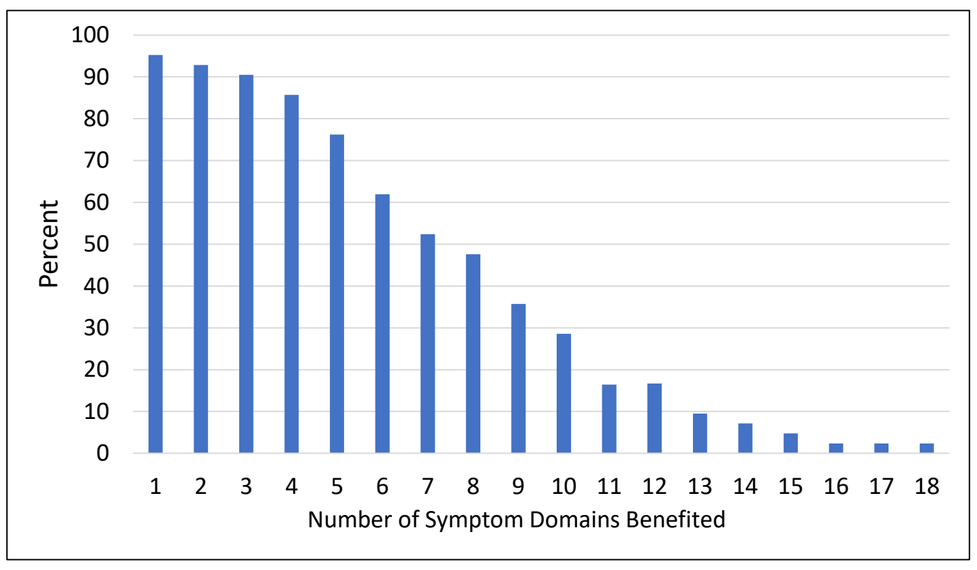


Fig 3 shows the percent of people without the symptom (in black), those with the symptoms but reporting no benefit (in purple), or different degrees of benefit (in blue, orange, green) at follow up.

Fig 3. Responder symptom domain benefit

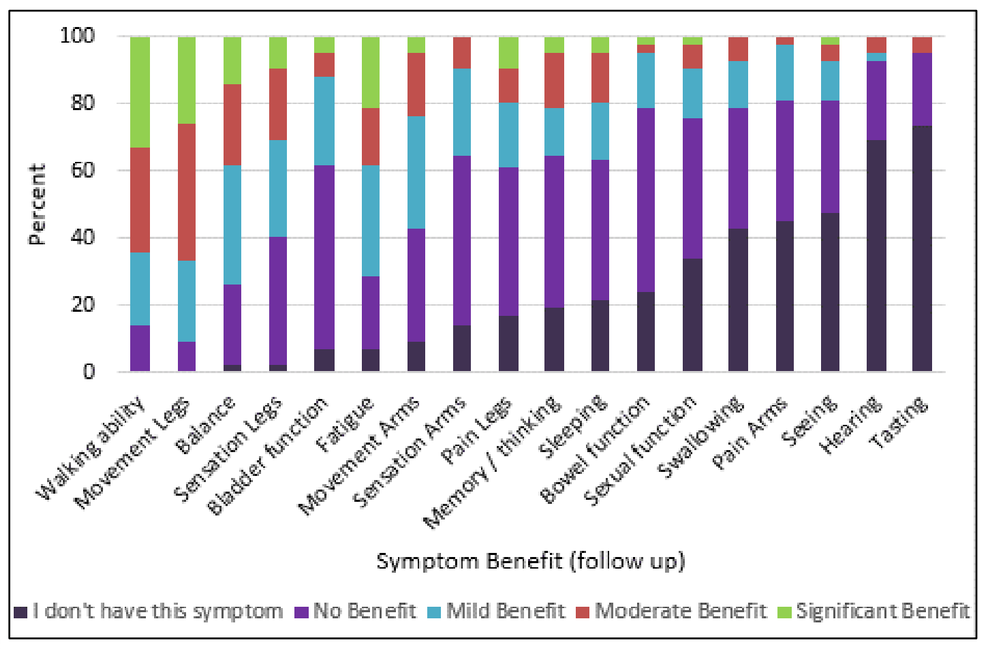
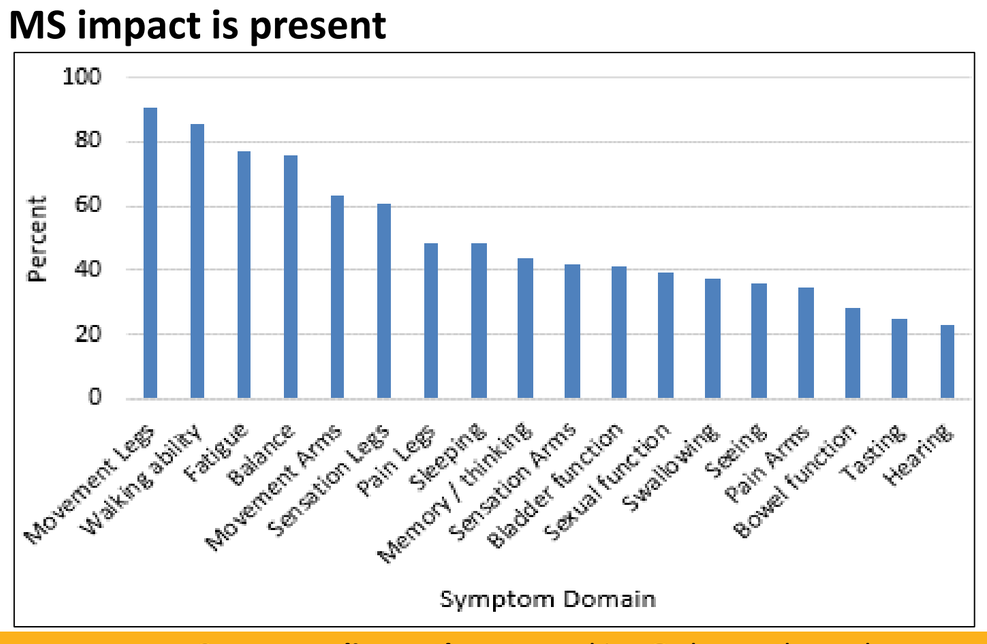


Fig 4 shows each impact domain was benefited by multiple individuals (range=23-90%, mean=50%).
Fig 4 shows the 6 MS impact domains were benefited by >60% participants; leg movement, walking, fatigue, balance, arm movement and leg sensation.

Fig 4. Percent of people reporting benefits when an MS impact is present



EQ-5D-3L and EQ-5D-5L Responder Results (Table 2)

- 37.5% improved their EQ-5D-3L HUI score. Of the remainder, 60% reported significant benefits in ≥1 MS impact domain (Table 3).
- 60% improved their EQ-5D-5L HUI score. Of the remainder, 50% reported significant impacts in ≥1 MS impact domain (Table 3).

Table 2. EQ-5D-3L and 5L results

RESPONDER	EQ-5D version and estimate			
	EQ-5D-3L		EQ-5D-5L	
	HUI[1,4]	Thermometer[4]	HUI[1,4]	Thermometer[4]
n	**40[5]**	**40[5]**	**40[5]**	**40[5]**
Possible score range	-0.594 to +1.0	0-100	-0.285 to +1.0	0-100
BASELINE				
Mean (SD)	0.47 (0.22)	46.40 (15.21)	0.53 (0.19)	46.40 (14.87)
Observed range	-0.074 to 0.814	10 to 75	0.087 to 0.892	10 to 75
FOLLOW-UP				
Mean (SD)	0.52 (0.22)	59.31 (17.81)	0.62 (0.19)	59.31 (17.81)
Observed range	0.087 to 0.892	10 to 90	-0.153 to 0.892	10 to 90
CHANGE				
Correlation: r(p)	0.44 (0.004)	0.44 (0.005)	0.62 (0.000)	0.45 (0.004)
Change: Mean (SD)	+0.06 (0.24)	+12.91 (17.64)	+0.09 (0.17)	+12.91 (17.41)
t (p)	+1.52 (0.14)	+4.63 (0.000)	+3.32 (0.002)	+4.69 (0.000)
Wilcox signed rank (*p*)	0.089	0.000	0.003	0.000
SRM[2]	+0.24	+0.73	+0.53	+0.74
Cohen's Effect Size[3]	+0.25	+0.85	+0.46	+0.87

[1] Health Utility Index
[2] SRM=standardised response mean = mean change/SD change
[3] Cohen's Effect size=mean change / SD baseline
[4] HUI and Thermometer: higher scores indicate better health, change computed as T2-T1 so that positive scores indicate improvement
[5] n=40 participants with complete EQ-5D data sets

Table 3. HUI score changes compared to MS Impact domain changes.

EQ-5D	Change	n=(%)	MS Domain Impact Questionnaire: Benefit >= 1 domain n= (%)	MS Domain Impact Questionnaire: Significant benefit >= 1 domain n= (%)
3L HUI	Worse	5/40 (12.5)	5/5 (100)	4/5 (80)
	Same	20/40 (50)	19/20 (95)	11/20 (55)
	Improved	15/40 (37.5)	14/15 (93.3)	9/15 (60)
5L HUI	Worse	9/40 (22.5)	9/9 (100)	5/9 (56.56
	Same	7/40 (17.5)	6/7 (85.7)	3/7 (42.86)
	Improved	24/40 (60)	23/24 (95.9)	16/24 (66.67)

Conclusion:

- Fampridine has widespread clinically meaningful benefits in MS beyond walking.
- Cost-effectiveness estimates based on EQ-5D, both -3L and -5L, can mislead.
- Results imply existing clinical trials may have underestimated Fampridine's effectiveness and cost-effectiveness.
- Qualitative insights provide a platform for future measurement strategies for evaluating drugs like Fampridine.
- Using EQ-5Ds to measure cost effectiveness should be reconsidered.

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Corresponding author: tanya.king@plymouth.ac.uk