The use of medical-grade Cannabis (Bedrocan®) in patients non-responders to Nabiximols

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INTRODUCTION

Spasticity is one of the most common symptoms in Multiple sclerosis (MS). Historical treatment includes several drugs with very limited patient and physician satisfaction. Nabiximols is a cannabis extract containing a 1:1 ratio of delta-9-tetrahydrocannabinol (THC) to Cannabidiol (CBD). Several studies showed its superiority over placebo in reducing the Numeric Rating Scale (NRS), a visual-analog-scale measuring the subjective impact of spasticity. Unfortunately, half of treated patients do not respond to Nabiximols and for them therapeutic options are absent.

METHODS

This was a retrospective observational study approved from the local Ethics Committee. Patients gave written informed consent before retrospective data collection. We selected patients that did not respond to 28 days of Nabiximols (reduction <20% from baseline NRS), and were subsequently treated with medical-grade cannabis (Bedrocan®) for at least 28 days. Eleven patients agreed to take Bedrocan in a Non-Activated Oral (NAO) formulation (Table 1), by direct ingestion of the inflorescence, without heating the drug. Two patients refused the NAO formulation, and decided to smoke Bedrocan.

To test the effect of Sativex and Bedrocan on the NRS, we used a Generalized Linear Model for Repeated Measures (GLM-RM), with repeated contrasts and Bonferroni correction. Partial eta squared (η^2) was used as a measure of effect size. Adverse events (AEs) were analyzed with a GLM with Poisson distribution.

Table 1. Demographics, clinical and Bedrocan data of treated patients

Pt.	Sex	Age	Onset	DMT	Antispastic medication	EDSS	Sativex dose	AE Sativex	AE Bedrocan	Bedrocan Dose (mg/day)	Bedrocan Route	Days on Bedrocan
1	M	42	37	No therapy	Baclofen	6.0	5	Drowsiness	-	50	NAO	46
2	M	42	25	Fingolimod	Baclofen	4.5	5	Confusion	-	50	NAO	321
3	F	56	50	Teriflunomide	Baclofen	6.5	8	Stomatitis	-	50	NAO	230
4	F	45	34	Natalizumab	Baclofen	6.5	12	Dizziness	Dizziness	50	NAO	224
5	F	53	31	Fingolimod	Baclofen	6.0	12	Nausea	Dizziness	50	NAO	168
6	M	64	49	Teriflunomide	Baclofen	6.5	6	Xerostomia	-	50	NAO	107
7	M	37	16	Fingolimod	Baclofen	5.0	8	Diarrhea, Ageusia, Drooling	-	100	NAO	91
8	M	48	27	Teriflunomide	Baclofen	6.5	12	Drowsiness, Incontinence	-	100	NAO	230
9	F	35	28	Fingolimod	Tizanidine	4.0	6	Dizziness, Weakness	-	50	NAO	46
10	F	38	19	No therapy	Baclofen	6.5	12	Confusion	Dizziness	100	S	700
11	M	44	24	Fingolimod	Baclofen	6.0	12	-	-	50	S	60
12	M	38	28	Interferon beta-1a	Baclofen	4.5	8	Xerostomia	-	75	NAO	369
13	M	45	27	Teriflunomide	Baclofen	7.5	6	-	-	50	NAO	83

Pt. = Patient; **DMT** = Disease Modifying Treatment; **EDSS** = Expanded Disability Status Scale; **AE** = Adverse Event; **NAO** = Non Activated Oral; **S** = Smoke

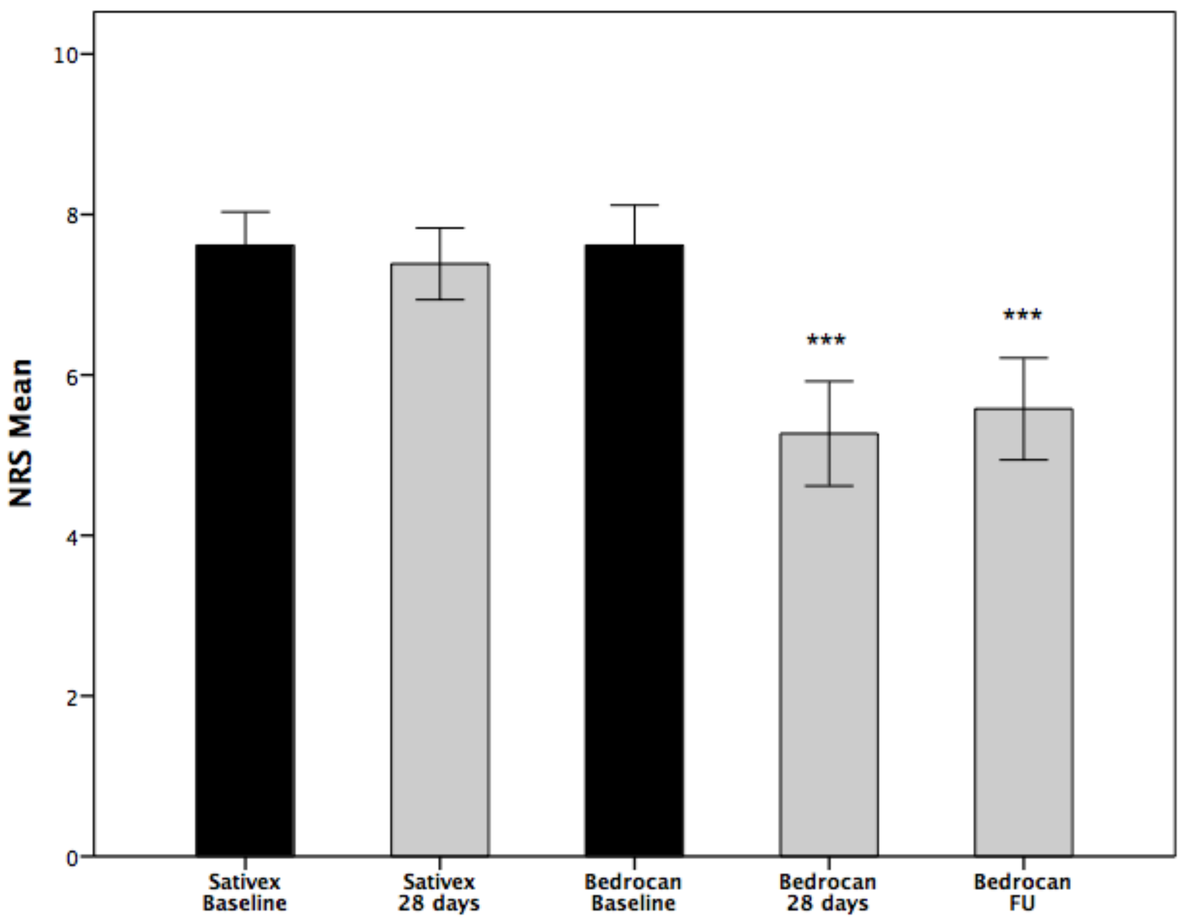
RESULTS

We found 13 patients corresponding to our criteria. Demographics and clinical data are shown in Table 1. Non-response to Nabiximols was caused by insufficient NRS reduction for all patients.

Mean NRS for Nabiximols Baseline was 7.6±1.5 and 7.4±1.6 after 28 days (-0.2; CI -0.65, +0.15; p=0.493). Mean NRS for Bedrocan baseline was 7.6±1.8 and 5.3±2.4 after 28 days (-2.3; CI -3.58, -1.12; p<0.001; η^2=0.75; Figure 1). Mean follow-up was 205±182 days (range 46-700). Two patients suspended therapy (pt. 10, 11), one for the onset of dizziness, and the other for the drug's cost. Mean NRS at follow-up was 5.6±2.3 (-2.0; CI -.2.9, -1.2; p<0.001; η^2=0.70; Figure 1).

Eleven patients (85%) were defined as responders to Bedrocan after 28 days of therapy, and 9 (70%) at follow-up. During Bedrocan therapy, only 3 AEs were reported in three patients, as compared to 15 AEs in 11 patients during Nabiximols treatment (Odds Ratio 5.0; CI 1.45, 17.27; p<0.02).

Figure 1. Cannabinoids and NRS



NRS = Numeric Rating Scale; **FU** = Follow-up; *** = p<0.001

CONCLUSIONS

Our rescue strategy with Bedrocan may be a promising therapy in Nabiximols non-responders. NAO formulation seems to be effective and better tolerated than Nabiximols. Future randomized, placebo-controlled trials are warranted to demonstrate, at a higher class of evidence, that medical-grade cannabis is a good option for Nabiximols non-responders.

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