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Non-invasive vagus nerve stimulation therapy for drug-resistant restless legs syndrome: six month follow-up

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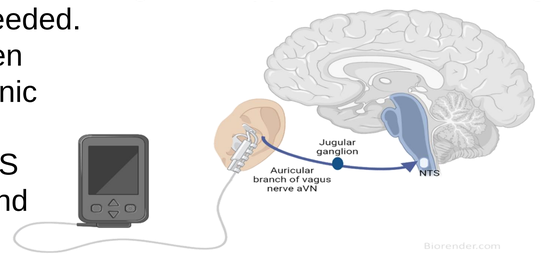
INTRODUCTION

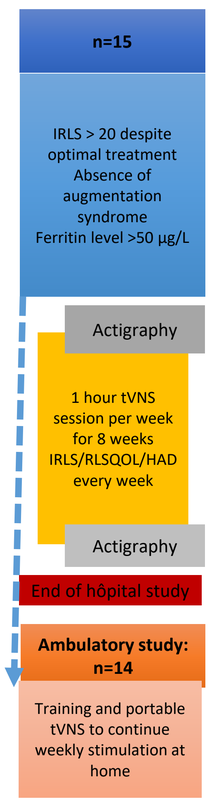
Severe pharmacoresistant restless legs syndrome (RLS) is difficult to manage and a source of suffering to patients. In some patients, despite optimal management including frequent changes of treatment, symptoms may remain difficult to control leading to considerable suffering. New approaches for treating pharmacoresistant RLS are urgently needed.
Vagus nerve stimulation (VNS) has been shown to be effective for epilepsy, chronic pain and depression.
The development of trans-auricular VNS (tVNS) avoids electrode implantation and has made VNS more accessible.



We recently published the first case series of tVNS for pharmacoresistant RLS (Hartley et al., 2023). In this non randomized study we showed symptom improvement in around two thirds of patients at eight weeks and a significant mean reduction in the IRLS score of 7,3. However outpatient tVNS is time consuming for patients and for practitioners. We developed a method for self-administration of tVNS at home to enable patients to continue their treatment long term.

The aim of this study was to evaluate the efficacy of tVNS at 6 months on RLS severity measured by the International restless legs rating score (IRLS) in patients self administering tVNS at home.

METHOD



Observational study of patients with pharmacoresistant RLS. All patients from the initial 8-week study were offered tVNS at home using portable stimulators with training in self-administration of tVNS. Inclusion criteria were severe (IRLS >20) pharmacoresistant RLS, with a ferritin >50 ng/ml. Patients with augmentation syndrome or taking more than the recommended doses of dopamine agonists (pramipexole > 0.36mg, ropinirole >=2 mg, rotigotine >=2 mg) were excluded.

Stimulation of the auricular branch of the vagal nerve was performed in the left anterior cymba conchae using a TENS eco Plus at 2Hz, 200µs symmetric square wave impulse width, and a titrated intensity from 2mA to 7mA. All patients were offered programmed portable stimulators and Schwa-Medico electrodes (reference 101012—101013/1). Patients were asked to perform tVNS for an hour once a week.

Outcome measures: Primary outcome measure: score on the International Restless Legs Rating Scale (IRLS). Secondary outcome measures: quality of life (RLSQOL), mood using the depression (HADD) and anxiety (HADA) subscales of the Hospital Anxiety and depression scale (HAD)

RESULTS

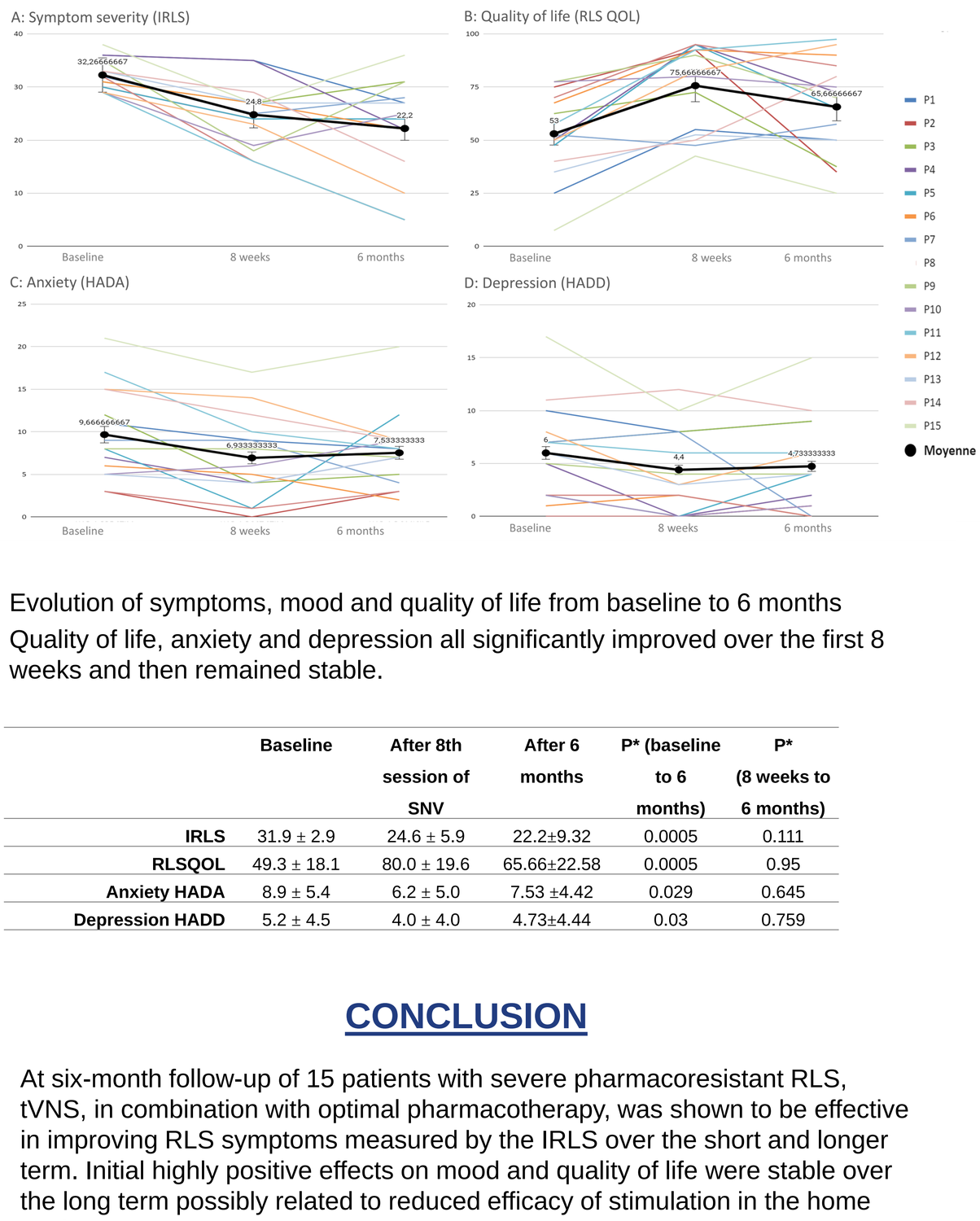
Population: Fifteen RLS patients, (53% male) aged from 27 to 74 years, mean 62.7 ±12.3 years, were included. All patients had severe RLS with a mean score of 31.9 ±2.9, and restless legs symptoms had been present on average for 15.5 +/- 8.6 years. Patients reported that their restless legs had a negative impact on their quality of life (RLSQOL 49.3 ± 18.1) and symptoms of depression (HADD 5.2 ± 4.5) and anxiety (HADA 8.9 ± 5.4) were present.

Patient	Sex	Age (years)	Duration of symptoms from start	Treatment	Hour of onset of symptoms with treatment	IRLS	RLSQOL	HADA	HADD	Mean Stimulation Intensity (mA)	Use of tVNS at home during 6 month follow-up
P1	M	73	38	Gabapentin, Tramadol, Codeine	20 :00	36	25	11	10	5	yes
P2	M	47	10	Gabapentin	00 :00	30	75	3	0	6	No
P3	M	72	17	Rotigotine	02 :00	31	62.5	12	7	5	Yes
P4	M	65	10	Pramipexole	19 :00	36	50	7	5	4	Yes
P5	F	73	15	Pramipexole Tramadol	16 :00	30	47.5	8	2	3	Yes
P6	M	71	19	Pregabalin Pramipexol, Tramadol	16 :00	31	67.5	6	1	4	Yes
P7	F	69	19	Pregabalin	18 :00	32	52.5	9	7	3	Yes
P8	M	62	11	Gabapentin	01 :00	32	70	3	2	5	Yes
P9	M	67	7	Pramipexole Gabapentin	00 :00	35	77.5	8	5	7	No
P10	F	62	14	Pregabalin Pramipexol, Tramadol	00 :00	29	77.5	5	2	4	Yes
P11	F	62	12	Gabapentin	21h00	29	57.5	17	7	5	Yes
P12	F	27	5	Gabapentin	20 :00	29	50	15	8	3	Yes
P13	M	69	29	Pregabalin Pramipexole, Codeine	13 :00	33	35	5	6	4	yes
P14	F	59	9	Pramipexole Gabapentin	19 :00	33	40	15	11	4	yes
P15	F	74	16	Pregabalin Pramipexole, Codeine	21 :00	38	7.5	21	17	6	yes

One patient refused home tVNS. 14/15 were given a home tVNS stimulator. 13/15 used their tVNS stimulator as advised.

RESULTS

The mean severity of symptoms of RLS measured by the IRLS was significantly reduced from baseline to session 8 and from baseline to 6 months (31.9 ± 2.9 vs 24.6 ± 5.9 vs 22.2±9.32 p=0.0005 respectively). with no significant change in the whole group from session 8 – 6 months. Ten out of the fifteen patients had an improvement >5 points on the IRLS, 4/15 patients had an IRLS <20 of whom 2/15 patients had a an IRLS at 6 months of 5 and effective disappearance of their symptoms.



Evolution of symptoms, mood and quality of life from baseline to 6 months

Quality of life, anxiety and depression all significantly improved over the first 8 weeks and then remained stable.

	Baseline	After 8th session of SNV	After 6 months	P* (baseline to 6 months)	P* (8 weeks to 6 months)
IRLS	31.9 ± 2.9	24.6 ± 5.9	22.2±9.32	0.0005	0.111
RLSQOL	49.3 ± 18.1	80.0 ± 19.6	65.66±22.58	0.0005	0.95
Anxiety HADA	8.9 ± 5.4	6.2 ± 5.0	7.53 ±4.42	0.029	0.645
Depression HADD	5.2 ± 4.5	4.0 ± 4.0	4.73±4.44	0.03	0.759

CONCLUSION

At six-month follow-up of 15 patients with severe pharmacoresistant RLS, tVNS, in combination with optimal pharmacotherapy, was shown to be effective in improving RLS symptoms measured by the IRLS over the short and longer term. Initial highly positive effects on mood and quality of life were stable over the long term possibly related to reduced efficacy of stimulation in the home setting.

Randomized controlled trials of tVNS in RLS are necessary to confirm a positive short and long term effect in RLS and to define optimal treatment modalities.

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