

Treat by Suggestion: The Potential Use of N = 1 Trials in Functional Neurological Disorders

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Functional neurological disorders (FND) are a common cause of refractory movement disorders.¹ In FND, in addition to processes such as sense of agency and abnormal attention, suggestibility in relation to the mechanism has been a topic of

discussion. A recent meta-analysis has shown patients with FND have an enhanced response to suggestion compared to controls.² This could play a role in making the diagnosis and providing treatment.

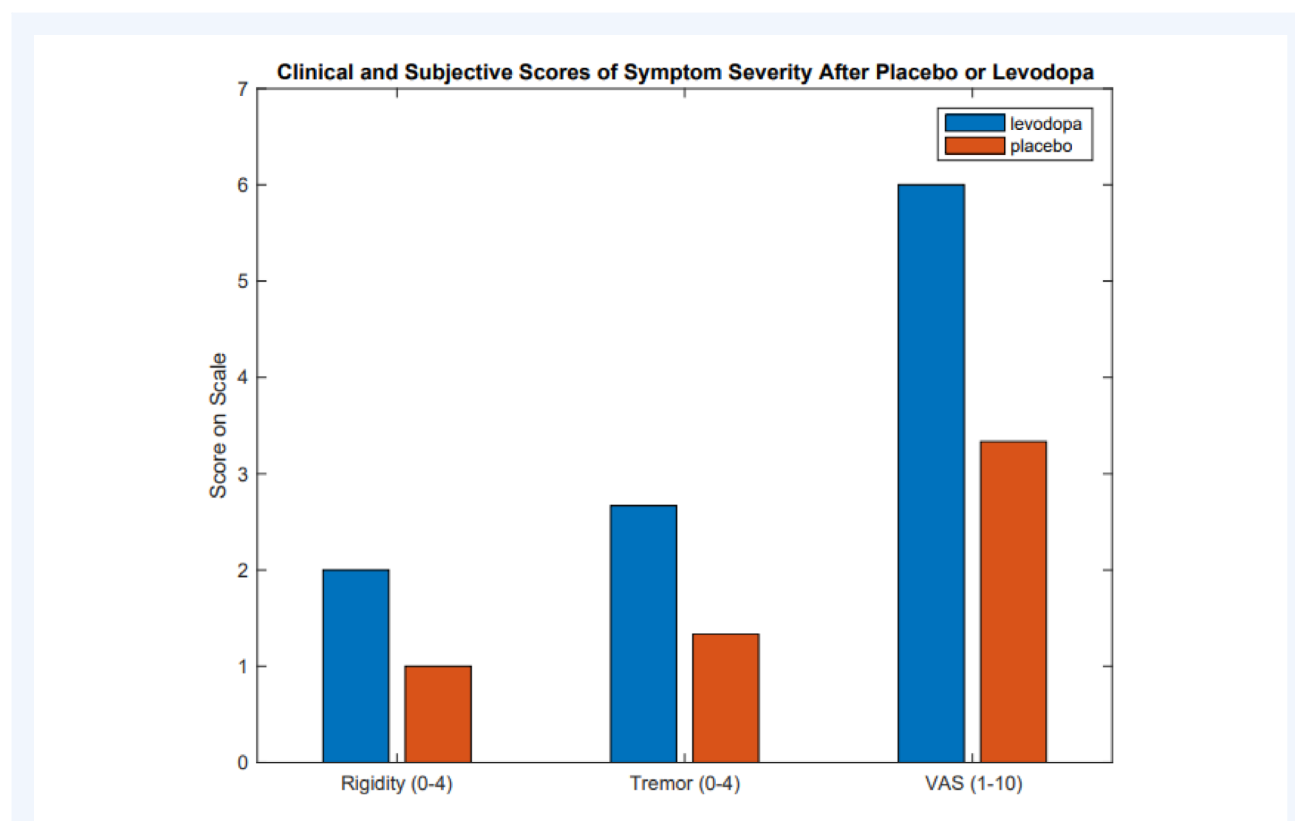


FIG. 1. Symptom severity scores after placebo or levodopa. Severity of symptoms measured by Visual Analogue Scale. Rigidity measured by Unified Parkinson's Disease Rating Scale rigidity items. Tremor measured by Fahn-Tolosa-Marin Scale tremor severity items.

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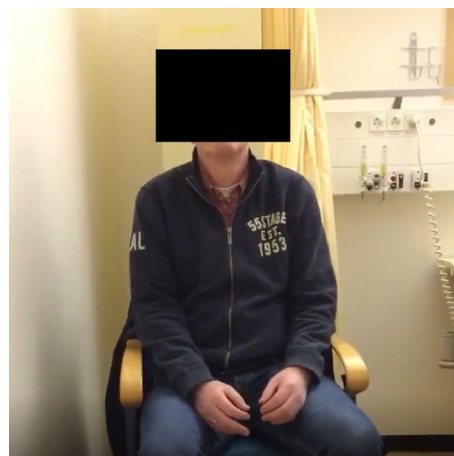
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Video 1. Effect of levodopa on tremor with and without cognitive co-activation, finger tapping and foot tapping. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13496>



Video 2. Effect of placebo on tremor with and without cognitive co-activation, finger tapping and foot tapping. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13496>

We describe a case of a patient with a refractory FND who did not accept his diagnosis, largely due to a placebo effect on levodopa. To persuade the patient to agree with his diagnosis, which is the prerequisite for treatment success,³ we performed a blinded trial to investigate whether this effect might be based on suggestion.

A 50 year old male with a history of Hashimoto thyroiditis and vitiligo presented with resting, postural and intention tremor and rigidity on the right arm and leg and anarthria for the last 19 years. At first presentation, the diagnosis of dopamine responsive dystonia was considered, and levodopa/carbidopa was started. Initially, patient experienced good effect of the medication. Due to increasing symptoms, he needed to increase the dose up to 200/50 mgs 7 times daily. However, the symptoms could no longer be fully suppressed. Given positive clinical signs of FND such as distractibility and entrainment, patient was diagnosed with FND. Ancillary investigations including a brain MRI, a ¹²³I-FP-CIT-scan, TSH, anti-thyroglobulin-antibodies and anti-thyroid-peroxidase-antibodies, were normal. We hypothesized that the positive effect was placebo induced and conducted a double-blind case study primarily to convince the patient so he could subsequently undergo FND treatment. Patient was informed about the randomization procedure.⁴

Levodopa/carbidopa and placebo capsules were produced with the same color and weight. Since the medication worked after approximately 45 minutes and stopped working after 2 hours, a trial design was made with 6 timepoints at which placebo or levodopa were given randomly.

Severity of symptoms was scored by a Visual Analogue Scale and by tremor and rigidity severity scores (Fig. 1). At three of the timepoints, the symptoms resolved completely (Videos 1 and 2). Deblinding revealed that 2 of these episodes were placebo induced. Based on this, patient accepted the diagnosis, agreed to discontinue treatment and was admitted for further treatment of FND in a specialized center. Hereafter, he showed improvement of his symptoms.

We report a patient with a placebo effect on FND in this double-blind n = 1 trial. To our knowledge, this is the first reported case illustrating this effect, emphasizing the effect of changing prior beliefs in treatment of FND. The cornerstone of treatment in FND is a cognitive behavioral model including sense of agency, change of body motor scheme, attention and illness beliefs. Prior beliefs have been suggested to play a role on shaping FND symptoms by overriding motor and perceptual systems based on recent theoretical models.⁵ Furthermore, this type of trial can also be used to increase diagnostic certainty. Since understanding and confidence in the diagnosis are the essential first step in treatment,³ in this case, the placebo-trial could be used as part of the cognitive model to explain the diagnosis and start treatment.

Author Roles

1) Research project: A. Conception, B. Organization, C. Execution, D. Data collection; 2) Manuscript preparation: A. Writing of the first draft, B. Review and Critique.

MU: 1B, 1C, 1D, 2A

JG: 2B

MB: 1A, 1B, 2B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Written and verbal informed consent from the patient was obtained and included in the patient record. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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