

Improvement of functional neurological disorder after administration of esketamine nasal spray: a case report

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Abstract: Functional neurological disorder (FND) is a complex neuropsychiatric condition characterized by the presence of neurological symptoms and signs (either motor or sensory) that cannot be explained by any known medical or mental disease. It is frequently presented with psychiatric comorbidities, such as major depression. Its prognosis is poor, with low improvement or recovery rates at 1 year after their onset, and no particular treatment has demonstrated significant efficacy in this regard. Here, we describe the management of a patient affected by treatment-resistant depression (TRD) and FND characterized by mixed paralysis (sensory and motor) in the left arm, and who was successfully treated with esketamine nasal spray, achieving remission in both disorders. The US Food and Drug Administration and the European Medicines Agency recently approved esketamine, the S-enantiomer of ketamine, for treatment of TRD. It is a fast-acting drug that provides a rapid-onset improvement of depressive symptoms. We have presented the first case, to our knowledge, of functional neurological symptoms being successfully treated with esketamine in a patient with comorbid TRD. While the novelty of this data implies a clear need for further research, it is suggested that esketamine might be a useful tool for the treatment of FND, acting through different theorized mechanisms that are in tune with recent advances in knowledge of the etiopathology of FND.

Keywords: esketamine, functional neurological disorder, treatment resistant depression, mixed paralysis

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Introduction

Functional neurological disorder (FND; also known as conversion disorder) is a complex neuropsychiatric condition characterized by the presence of one or more symptoms (either motor or sensory) that cannot be explained by any known medical or mental health condition, and that causes significant distress in different areas (e.g. social, occupational). Importantly, and as outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders,¹ these symptoms are not deliberately generated or feigned by the patient; and although FND has been traditionally viewed as an exclusion diagnosis, new models based on the most recent evidence have proposed a positive diagnosis based on specific neurological signs, such as Hoover's sign.^{2,3}

Evidence suggests a prevalence of up to 4–11 per 100,000 in the general population, increasing to 11–22 per 100,000 in primarily psychiatric settings, and reaching an estimation of 20% of all patients being treated at a neurologic outpatient clinic.^{4,5}

Moreover, comorbidity with other psychiatric disorders is common; depressive and anxiety disorders being the most frequently found diagnoses. Personality disorders are also prevalent in these patients, as well as somatic symptoms disorders, and other medical and neurological disorders such as epilepsy.¹

FND presents a poor outcome and prognosis, with low improvement and recovery rates 1 year after onset. In most studies, functional motor

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symptoms and functional seizures are the same or worse in the majority of patients at follow up, and the long duration of symptoms seems to be the most relevant predictor of a negative outcome.⁶

Despite the high prevalence and poor prognosis of this disorder, there is still a scarcity of effective options and no standard protocol for the treatment of FND. Two recent Cochrane reviews on the efficacy of pharmacological and non-pharmacological treatments for somatic symptom disorder, which include FND, concluded that only cognitive-behavioral therapy (CBT) might be more effective than placebo, although the effect size was small. No clear differences were found between any drug and placebo.^{7,8} Although randomized clinical trial evidence is limited, promising data are emerging, and a greater role for physical therapy has recently been recognized when motor symptoms predominate. Treatment of the aforementioned comorbidities frequently present in FND is also fundamental to a better outcome.²

According to the World Health Organization, major depressive disorder (MDD), the most common comorbidity of FND, is the leading cause of disability worldwide. Even with the many treatment options available for MDD, up to one third of patients do not adequately respond. Esketamine nasal spray (the S-enantiomer of racemic ketamine) has been developed as an antidepressant with a novel mechanism of action and has recently been approved for treatment-resistant depression (TRD). This glutamate-receptor antagonist selectively blocks N-methyl-D-aspartate receptors expressed on gamma-aminobutyric-acidergic inhibitory interneurons, leading to enhanced glutamatergic firing. This increases α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor stimulation, leading to an array of molecular and cellular events, including increases in brain-derived neurotrophic factor (BDNF) expression. These changes are thought to induce production of synaptic proteins and synaptogenesis, and eventually restoration of synaptic function.⁹

The dosing schedule for esketamine nasal spray is different from previous treatments for TRD. It is divided into an induction phase and a maintenance phase. In the 4-week induction phase, dosing is flexible, with different doses recommended twice weekly depending on age and ethnicity. The maintenance phase begins after the initial 4 weeks, in which esketamine nasal spray can be administered flexibly: once a week, or every other week.¹⁰

We describe here the management of a patient affected by TRD and functional neurological disorder characterized by mixed paralysis (sensory and motor) in the left arm, who improved upon receiving treatment with esketamine nasal spray. To our knowledge, this indication has not been reported before in the literature.

Case report

We present a 49-year-old man with a history of chronic hypertension and a psychiatric history of MDD that was first diagnosed 20 years ago, whereupon he received treatment with paroxetine with good response, with later treatment withdrawal without relapse.

He was admitted to the psychiatric emergency room at Vall d'Hebron University Hospital on October 2019 with a major depressive episode and limited mobility of the left limb, without identifying any potential triggering event. Neurological symptoms (of sudden onset) were characterized by a mixed paralysis (sensory and motor) affecting the left extremity, and were assessed by a psychiatrist and a neurologist. Complementary explorations were performed, including computed tomography, nuclear magnetic resonance and electromyography, without pathological findings. Given the clinical features characterized by rapid onset, attenuation with distraction and increase with attention, as well as incongruence with the results of complementary tests, a FND was diagnosed, with paralysis of the left extremity. This was the first episode of functional paralysis and sensory loss for this patient.

Upon first consultation, the patient was not receiving any pharmacological treatment. Paroxetine was prescribed, initially 20 mg/day and increased to 60 mg/day over the following month, adding up to 0.5 mg/8 h clonazepam, with little response.

In January 2020, mirtazapine 15 mg was added at night, and boosted with aripiprazole 15 mg/day, together with the start of CBT in February 2020. CBT sessions were performed every 2 weeks and are ongoing; the main objective was to treat depression symptoms, but functional neurological symptoms were also addressed. During the ensuing months, the patient presented partial improvement of the depressive symptoms, but the functional neurological symptomatology persisted. In June 2020, we decided to switch the antidepressant to venlafaxine, up to 300 mg/day; again, with little response.

In October 2020, we proposed treatment with esketamine nasal spray to the patient, who agreed and provided written informed consent for the treatment as well as publication of their medical data.

Before starting treatment, paresis of the left extremity had persisted for 1 year, concurrent with numbness. There was a significant loss of strength and mobility, and major functional limitations and loss of autonomy, as a result of which, the patient needed help with everyday activities.

Esketamine nasal spray medication was initiated on treatment day 1, beginning at a dose of 56 mg administered using two nasal spray devices (28 mg per device) with good tolerance, so on day 2, the dose was increased to 84 mg (three nasal spray devices). Thereafter, the patient received treatment at a dose of 84 mg twice a week for 4 weeks.

After administration of esketamine, the patient presented mild dissociative symptoms. At 2 h after administration, the patient reported complete remission of dissociative symptomatology without presenting other adverse effects.

The patient responded to the treatment from the first session with improvement of depressive symptoms. He is still in maintenance treatment, taking esketamine every 2 weeks, and, after 5 months' follow up, his depressive symptoms continue in remission (as shown in the Montgomery-Åsberg Depression Rating Scale in Figure 1).

Also, from the first treatment session, the patient presented an improvement in mobility of the left superior extremity, which persists. He has recovered full mobility, uses his limb in daily activity, and presents a 5/5 muscular strength, assessed using the Medical Research Council power grade. His numbness has also fully disappeared.

Administered treatments and symptom progression over time are summarized in Figure 2.

It should be noted that, during the first 2 h after administration, the patient presented an almost complete recovery of mobility, which slightly worsened a few days after the treatment session, although he was still able to perform tasks he was unable to before, and with a persistent increase in autonomy for daily activities, through to the present day.

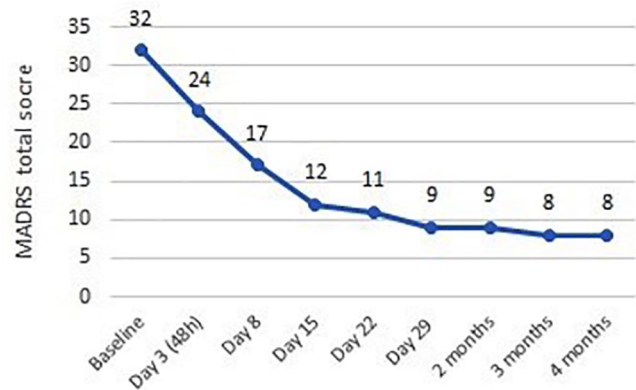


Figure 1. Evolution of the MADRS total score. MADRS, Montgomery-Åsberg Depression Rating Scale.

Discussion

To our knowledge, this is the first reported case of FND improvement after treatment with esketamine in a patient with comorbid TRD.

Esketamine has recently been approved for the treatment of TRD. In addition to its antidepressant properties, esketamine is unique, as it allows rapid-onset improvement of depressive symptoms.¹¹ It is the S-enantiomer of racemic ketamine, a well-known drug that has recently been shown to have robust antidepressant effects.⁹ However, primary use of ketamine was based on its anesthetic properties; it is still widely used for the treatment of chronic pain, and in critical care and surgical settings.¹²

Interestingly, ketamine and esketamine also have remarkable psychoactive effects, which might be related to their antidepressant properties.¹³ The degree of dissociation, depersonalization, and derealization induced by ketamine also seems to be related to the degree of response in depressed patients.¹⁴

While the novelty of this data clearly requires careful consideration of its implications, it suggests that esketamine might be a useful tool for the treatment of functional neurological disorders. We propose the possible involvement of the following action mechanisms that might be involved.

First, in the case reported, the patient showed an improvement in depressive symptoms, parallel to the reversion of his functional motor symptoms. While there is insufficient evidence to support a causal correlation between psychiatric disorders

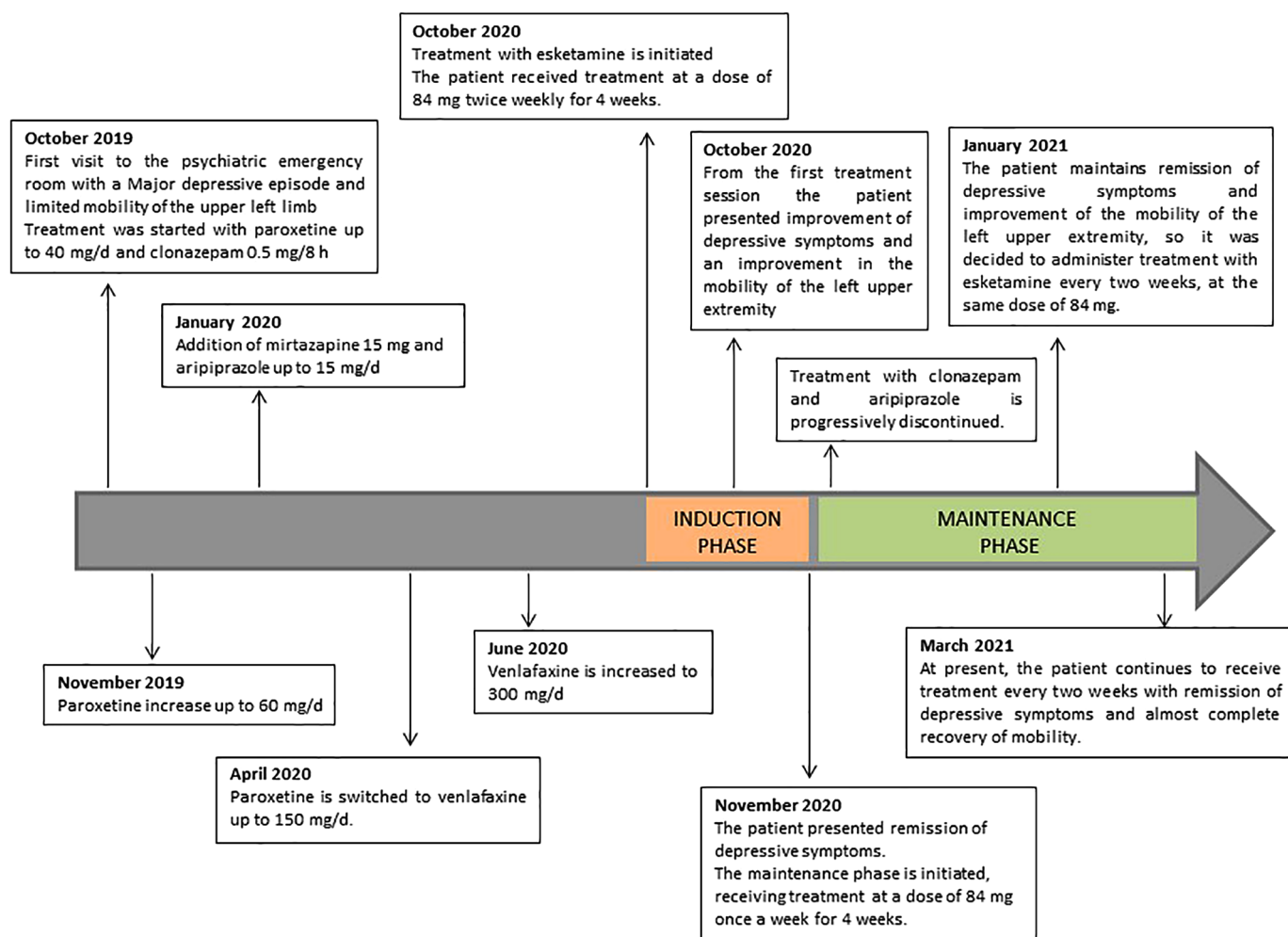


Figure 2. Symptom evolution and treatment administration through time.

and functional neurological symptoms, the latter are more prevalent in people presenting with the former. Moreover, the presence of stressors is known to be relevant, although not sufficient nor necessary, for the onset of both disorders.¹

In line with the theory that there is a relationship between depression and FNDs, antidepressants are widely used for its treatment, although there is insufficient evidence to support this practice, and they should only be used when there is a comorbid psychiatric illness.⁷

Regarding esketamine, some studies suggest that it could improve brain plasticity *via* the stimulation of BDNF production and activation of the mammalian target of rapamycin (mTOR) pathway. Modulation of mTOR would stimulate additional BDNF production, resulting in increased

brain plasticity (dendritic growth and improved synaptic transmission). Esketamine could have a more direct stimulation effect on BDNF and mTOR than the present oral ADs. This may explain the rapid onset of esketamine's effect, and also why the effects are maintained even after drug elimination.^{15,16} In our case, the patient presented a rapid improvement in depressive symptoms, which was maintained for the following days, as well as a rapid improvement in functional neurological symptoms, although in this case, there was a slight loss of effect between doses. This further reinforces the theory that the mechanisms of action for improvement are similar in the two disorders, although more frequent doses might be needed in functional neurological disorders.

Secondly, several theories have attempted to ascertain the neurobiological basis of FND, with

conflicting findings. However, emotional circuits, (mainly limbic networks), and their influence on the regulation of cortico–striato–thalamo–cortical circuits, are thought to be relevant.¹⁷ Classic psychedelics, which act through serotonergic agonism, but have similar downstream effects to esketamine *via* glutamatergic neurotransmission, have recently been proposed as plausible candidates to treat FND.^{18,19} One of the main theoretical frameworks in this regard lies in their capacity to influence neural networks, especially the default mode network.²⁰

Thirdly, patient beliefs about their own symptoms seem to be important for prognosis of functional neurological symptoms.²¹ It has also been thought that FND and hypnotic states bear a resemblance to each other, and some recent evidence points in this direction, suggesting that self-awareness and self-imagery play a central role in this disorder.²² Suggestion techniques and altered states of consciousness such as those provided by esketamine, would foster a change in the patient's prior beliefs that could influence his/her self-imagery.²³

Finally, while neither ketamine or esketamine have, to our knowledge, been tested before for functional neurological symptoms, ketamine has been shown to be efficacious for treating chronic pain,²⁴ a condition that overlaps in several aspects with FND, and that has been shown to respond to similar treatments,²⁵ which points to a possible role of their analgesic effects. Other dissociative anesthetics have also been tested for treatment of FNDs, with promising results, which further reinforces the possible role of the proposed mechanisms of action.²⁶

Conclusion

To our knowledge, this is the first report of an improvement in functional neurological symptom disorder in a patient affected by a comorbid TRD after treatment with esketamine. The novelty of this data warrants the need for further evidence on the use of esketamine for this indication. However, the absence of valid treatment options and the poor prognosis of FND should encourage further research in this direction.

The most recent findings on the etiology of this condition might support the efficacy of this compound.

Conflict of interest statement

J.Vendrell-Serres has received fees from Lundbeck, Janssen and Angelini to act as speaker or consultant. J.A.R.Q. was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogi, Sincrolab, Novartis, BMS, Medice, Rubió, Uriach and Raffo in the last 3 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogi, Bial and Medice. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 3 years: Janssen-Cilag, Shire, Oryzon, Roche, Psious, and Rubió. O. Soto-Angona, A. Rodríguez-Urrutia and G. Arteaga-Henríquez report no conflict of interest.

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References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association, 2013.
2. Espay AJ, Aybek S, Carson A, *et al.* Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 2018; 75: 1132–1141.
3. Stone J, Burton C and Carson A. Recognising and explaining functional neurological disorder. *BMJ* 2020; 371: m3745.
4. Feinstein A. Conversion disorder. *Continuum (Minneapolis)* 2018; 24: 861–872.
5. Stone J, Carson A, Duncan R, *et al.* Who is referred to neurology clinics? – the diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 2010; 112: 747–751.
6. Gelauff J and Stone J. Prognosis of functional neurologic disorders. In: Hallet M, Stone J and Carson A, (eds) *Handbook of clinical neurology*. 1st ed. Elsevier B.V., 2016, Vol. 139, pp.523–541.

7. Kleinstäuber M, Witthöft M, Steffanowski A, *et al.* Pharmacological interventions for somatoform disorders in adults. *Cochrane Database Syst Rev* 2014; 11: CD010628.
8. Van Dessel N, Den Boeft M, Van der Wouden JC, *et al.* Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. *Cochrane Database Syst Rev* 2014; 11: CD011142.
9. Kasper S, Cubała WJ, Fagiolini A, *et al.* Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: basic science, evidence-based knowledge and expert guidance. *World J Biol Psychiatry*. Epub ahead of print 12 November 2020. DOI: 10.1080/15622975.2020.1836399.
10. EMA. Spravato® (esketamine) summary of product characteristics (Internet), https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf (2019, accessed 23 January 2021).
11. Molero P, Ramos-Quiroga JA, Martin-Santos R, *et al.* Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs* 2018; 32: 411–420.
12. Kurdi M, Theerth K and Deva R. Ketamine: current applications in anesthesia, pain, and critical care. *Anesth Essays Res* 2014; 8: 283.
13. Mathai DS, Meyer MJ, Storch EA, *et al.* The relationship between subjective effects induced by a single dose of ketamine and treatment response in patients with major depressive disorder: a systematic review. *J Affect Disord* 2020; 264: 123–129.
14. Niciu MJ, Shovestul BJ, Jaso BA, *et al.* Features of dissociation differentially predict antidepressant response to ketamine in treatment-resistant depression. *J Affect Disord* 2018; 232: 310–315.
15. Ignácio ZM, Réus GZ, Arent CO, *et al.* New perspectives on the involvement of mTOR in depression as well as in the action of antidepressant drugs. *Br J Clin Pharmacol* 2016; 82: 1280–1290.
16. Sattar Y, Wilson J, Khan AM, *et al.* A review of the mechanism of antagonism of N-methyl-D-aspartate receptor by ketamine in treatment-resistant depression. *Cureus* 2018; 10: e2652.
17. Del Río-Casanova L, González A, Páramo M, *et al.* Excitatory and inhibitory convergent experiences: neurobiological features involving positive and negative conversion symptoms. *Rev Neurosci* 2016; 27: 101–110.
18. Bryson A, Carter O, Norman T, *et al.* 5-HT_{2A} agonists: a novel therapy for functional neurological disorders? *Int J Neuropsychopharmacol* 2017; 20: 422–427.
19. Butler M, Seynaeve M, Nicholson TR, *et al.* Psychedelic treatment of functional neurological disorder: a systematic review. *Ther Adv Psychopharmacol* 2020; 10: 204512532091212.
20. Stewart B, Dean JG, Koek A, *et al.* Psychedelic-assisted therapy for functional neurological disorders: a theoretical framework and review of prior reports. *Pharmacol Res Perspect* 2020; 8: e00688.
21. Sharpe M, Stone J, Hibberd C, *et al.* Neurology out-patients with symptoms unexplained by disease: illness beliefs and financial benefits predict 1-year outcome. *Psychol Med* 2010; 40: 689–698.
22. Vuilleumier P. Brain circuits implicated in psychogenic paralysis in conversion disorders and hypnosis. *Neurophysiol Clin* 2014; 44: 323–337.
23. Carhart-Harris RL and Friston KJ. REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. *Pharmacol Rev* 2019; 71: 316–344.
24. Cohen SP, Bhatia A, Buvanendran A, *et al.* Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018; 43: 521–546.
25. Tsui P, Deptula A and Yuan DY. Conversion disorder, functional neurological symptom disorder, and chronic pain: comorbidity, assessment, and treatment. *Curr Pain Headache Rep* 2017; 21: 29.
26. Stone J, Hoeritzauer I, Brown K, *et al.* Therapeutic sedation for functional (psychogenic) neurological symptoms. *J Psychosom Res* 2014; 76: 165–168.