HAL
open science

Approval of esketamine for treatment-resistant depression - Authors' reply

Florian Naudet, Ioana A Cristea

To cite this version:

Florian Naudet, Ioana A Cristea. Approval of esketamine for treatment-resistant depression - Authors' reply. The Lancet. Psychiatry, 2020, 7 (3), pp.235-236. 10.1016/S2215-0366(20)30040-7 . hal-02498635

HAL Id: hal-02498635

https://univ-rennes.hal.science/hal-02498635

Submitted on 12 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Approval of esketamine for treatment-resistant depression -Author Reply

Florian Naudet, MD, Ph.D.

University Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France, e-mail : floriannaudet@gmail.com

Ioana A. Cristea

Department of Department of Brain and Behavioral Sciences, University of Pavia, Piazza Botta 11, 27100 Pavia, Italy, email: ioana.cristea@unipv.it

Accepted Manuscript

We acknowledge Janssen's reply to concerns raised about the regulatory process that brought esketamine for treatment-resistant depression (TRD) on the market. We regret the lack of response from the Food and Drug Administration. We forwarded our concerns to the Committee for Medicinal Products for Human Use of the European Medicine Agency, whose written response elaborated on the same main arguments as Janssen's reply.

Pivotal in both replies is the notion of minimal clinically important difference (MCID, i.e. the smallest change in outcome to qualify as important). Specifically, a MADRS difference of 2 points is denoted as clinically meaningful, even when statistically not significant, an astonishing claim that undercuts the rationale of significance testing altogether. Nevertheless, measuring and establishing a MCID is contentious, with both lower (i.e., 2 MADRS points)[1] and higher threshold (i.e., 7-9 points)[2] proposed. Moreover, any threshold must be selected on a case-by-case basis, weighing the drug's potential for harms and context of use. As esketamine carries well-known risks, this threshold should be nominally higher and, for a chronic condition like TRD, observing improvements at 4 weeks is insufficient. A meaningful MCID should be reported versus existent treatment alternatives (psychotherapy, electroconvulsive treatment).

Moreover, the pre-specified MADRS difference used for sample size calculations in the three initiation trials (TRD3001[3], TRD3002[4], TRD3005[5]) was 6.5, meaning that for differences below this threshold, it was considered acceptable to risk overlooking an effect. A meta-analysis of the pivotal esketamine trials[6] reported a summary estimate versus placebo of 4.08 MADRS points [95% CI 1.99 to 6.18], again below the *a priori* threshold of 6.5 points.

A posteriori debates on appropriate thresholds are impossible to settle. Conversely, we believe regulatory science could benefit from the model of *a priori* registration, such as "registered drug approvals", following the "data-blind" peer-review model of registered reports (https://cos.io/rr/). With adequate success criteria, this model would guarantee transparency in establishing the threshold employed in defining meaningful change.

Authors' contributions

IAC and FN conceived, drafted and revised the manuscript.

Declaration of interest

IAC and FN have no conflicts of interest to disclose.

References:

1. Duru G, Fantino B. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. *Current medical research and opinion* 2008; **24**(5): 1329-35.

Accepted Manuscript

2. Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercentile linking with the CGI using a company database of mirtazapine studies. *Journal of Affective Disorders* 2017; **210**: 287-93.
3. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *International Journal of Neuropsychopharmacology* 2019; **22**(10): 616-30.
4. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry* 2019; **176**(6): 428-38.
5. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2019.
6. Gastaldon C, Papola D, Ostuzzi G, Barbui C. Esketamine for treatment resistant depression: a trick of smoke and mirrors? *Epidemiology and psychiatric sciences* 2019; **29**: e79.

Accepted Manuscript