Epidemiology and Psychiatric Sciences

cambridge.org/eps

Epidemiology in Clinical Psychopharmacology

This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the role of the epidemiological approach to promote advances in the field of clinical psychopharmacology, with a particular attention to controversial findings. The ultimate aims are to help develop a more critical attitude towards the results of research studies published in the international literature, to promote original research projects with higher methodological standards, and to implement the most relevant results of research in every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, 4 key-words, one Table or Figure and up to ten references).

Corrado Barbui, *Section Editor*

Cite this article: Mathews M, Daly EJ, Popova V, Heerlein K, Canuso C, Drevets WC (2020). Comment to Drs Gastaldon, Papola, Ostuzzi and Barbui. *Epidemiology and Psychiatric Sciences* **29**, e124, 1–3. https://doi.org/10.1017/S2045796020000268

Received: 13 February 2020
Revised: 13 February 2020
Accepted: 3 March 2020

Author for correspondence:
Maju Mathews, E-mail: mmathe20@its.jnj.com

CAMBRIDGE UNIVERSITY PRESS

Comment to Drs Gastaldon, Papola, Ostuzzi and Barbui

Maju Mathews[1], Ella J. Daly[2], Vanina Popova[3], Kristin Heerlein[4], Carla Canuso[5] and Wayne C. Drevets[6]

[1]Neuroscience Global Medical Affairs, Janssen Research & Development, LLC, Titusville, NJ, USA; [2]Department of Clinical Medical Affairs, Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [3]Department of Neuroscience, Janssen Research & Development, Beerse, Belgium; [4]Department of Medical and Scientific Affairs, Neurosciences, Janssen EMEA, Neuss, Germany; [5]Department of Neuroscience, Janssen Research & Development, LLC, Titusville, NJ, USA and [6]Department of Neuroscience, Janssen Research & Development, LLC, San Diego, CA, USA

We appreciate the questions raised by Gastaldon *et al.* (2020) in *Epidemiology and Psychiatric Services* about esketamine's efficacy and the study designs within the clinical development programme for treatment-resistant depression (TRD), and provide clarification herein.

Dr Gastaldon and associates acknowledged that the TRANSFORM-2 study (Popova *et al.*, 2019) (short-term, flexible dose) achieved statistical significance, and commented that two other short-term, randomized controlled studies of esketamine nasal spray (Fedgchin *et al.*, 2019; Ochs-Ross *et al.*, 2020) 'showed similar mean differences in change scores without statistical significance'. The prespecified, primary efficacy endpoint analysis in all three cited studies was the mean difference (based on mixed-model repeated-measures analysis) between the esketamine plus oral antidepressant group *v.* the oral antidepressant plus placebo nasal spray group on change from baseline in Montgomery–Asberg Depression Rating Scale (MADRS) total score at day 28.

Dr Gastaldon and co-authors report on a *post hoc* re-analysis they conducted of the primary efficacy data from the three phase 3 short-term studies, for which they report an overall mean difference of −4.08 (95% CI −6.20 to −1.97). However, they claim incorrectly that this mean difference falls short of clinical significance.

All three short-term efficacy studies, including the two that did not show statistical significance on the primary endpoint [TRANSFORM-1 (Fedgchin *et al.*, 2019) and TRANSFORM-3 (Ochs-Ross *et al.*, 2020)] demonstrated between-group mean differences relative to the comparator (a new oral antidepressant plus placebo nasal spray), with regard to the change in MADRS total score, which exceeded the mean difference that is considered clinically relevant in the psychiatric literature, namely 2.0 points or higher (Montgomery and Möller, 2009). This threshold also has been used as a criterion for establishing clinically meaningful benefit by European Health Authorities (Melander *et al.*, 2008). Further, the US Food and Drug Administration (FDA) [Medical Review, Table 62 (Food and Drug Administration, 2019)] notes that despite evaluation in a study population with greater illness severity, the magnitude of improvement on the MADRS (primary endpoint) with esketamine nasal spray plus oral antidepressant as compared to oral antidepressant plus placebo nasal spray is similar to that achieved by other approved antidepressants that were compared only to placebo. FDA's review additionally refers to secondary patient-reported depression [the 9-item Patient Health Questionnaire (PHQ-9)] and functional outcome [the Sheehan Disability Scale (SDS)] measures, which also indicated consistent benefit with esketamine plus oral antidepressant over oral antidepressant plus placebo nasal spray across all phase 3 studies (with nearly all showing at least numerical improvement), providing further support for the clinical meaningfulness of the efficacy findings.

Notably, one reason Gastaldon *et al.* provide for questioning the clinical relevance of the between-group mean differences in MADRS ratings obtained in the short-term esketamine trials was based on an apparent error in their reading of data provided in prior articles by our group. Specifically, they state: 'The authors of the three studies reported that a difference of at least 6.5 points at MADRS between esketamine and placebo should be observed to make a claim of clinical significance…'. However, the value of 6.5 points provided in those articles was never stated to be a cut-off for clinical relevance. Instead, the 6.5-point value clearly referred to the *estimated* difference that was used in power calculations performed to estimate the sample size for the short-term phase 3 trials, which was based on results from an earlier adjunctive phase 2 trial (Daly *et al.*, 2018). In that phase 2 trial, the interventions were esketamine nasal spray *v.* placebo nasal spray, each added to an ongoing oral antidepressant drug to which the patient had already proven non-responsive. In contrast, in phase 3 trials, both esketamine and placebo nasal spray were combined with a newly added oral antidepressant to which the patient had *not* previously proven non-responsive. This design difference presumably contributed to the larger effect size in our phase 2 *v.* phase 3 trials.

In addition, while referring to data for mean change from baseline, the authors incorrectly state that the treatment effect observed at week 4 in the TRANSFORM-2 study is not related to esketamine because 'a clinically important reduction in the MADRS score was detected also in the placebo group'. The change from baseline in the 'placebo' arm, however, must be interpreted in the context of being an active, 'standard-of-care' control condition in which patients received a newly added oral antidepressant along with placebo nasal spray. The TRANSFORM-2 trial demonstrated a between-treatment group mean difference in MADRS total score of −4.0 points at the primary endpoint (day 28) as well as of −3.3 points at day 2 (24 h after a single dose), a time-point when the effect of a newly initiated oral antidepressant would unlikely have had an impact. Furthermore, the mean difference between esketamine and comparator group observed at day 2 generally remained through day 28.

Gastaldon and associates also commented 'for esketamine, long-term data are lacking'. However, Janssen included two long-term studies of esketamine in the phase 3 programme based on the fact that the FDA (Kim *et al*., 2019) and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency, 2010) both required short-term and long-term data in the initial marketing authorization application. Note that the FDA generally requires only short-term studies for initial approval of antidepressants; long-term studies are typically conducted after approval to support a maintenance indication (Kim *et al*., 2019). The two phase 3 registration trials [SUSTAIN-1 (Daly *et al*., 2019); SUSTAIN-2 (Wajs *et al*., 2020)] assessed the maintenance of antidepressant effects beyond the initial acute treatment period with esketamine nasal spray in adult patients with treatment-resistant MDD (Food and Drug Administration, 2019). On the basis of findings from the relapse prevention study (SUSTAIN-1), esketamine nasal spray is approved for maintenance treatment of patients with TRD (Spravato™ 2019). In addition, the phase 3 programme included an open-label safety and efficacy study of up to 1 year in duration [SUSTAIN-2 (Wajs *et al*., 2020)]. The results of SUSTAIN-2 support those from SUSTAIN-1, and based on the safety data, provide further evidence to support long-term, intermittent dosing with esketamine.

Gastaldon and associates were specifically critical of the randomized withdrawal design of SUSTAIN-1 (Daly *et al*., 2019), a design recommended by many health authorities for relapse prevention trials (European Medicines Agency, 2010; US Department of Health and Human Services, Food and Drug Administration, 2018). This study design was discussed and agreed upon with both the FDA and the CHMP. The aim of SUSTAIN-1, which the authors mention in their Commentary, was to determine whether the antidepressant effect in patients who had achieved stable remission with repeated-interval dosing of esketamine in combination with an oral antidepressant after 16 weeks (4 weeks induction plus 12 weeks of optimization) could be maintained with continued treatment, or whether esketamine could be discontinued and response maintained on an oral antidepressant alone. Given the study's objective, the population was necessarily enriched. Gastaldon *et al*. state that 'this type of design tends to overemphasize the efficacy of maintenance treatment, as the comparison group is at extremely high risk of relapse, considering that treatment is abruptly stopped soon after treatment.' However, in SUSTAIN-1, all patients continued their ongoing oral antidepressant: Patients with TRD who achieved stable remission and those who achieved stable response (without remission) with esketamine nasal spray were randomized to continue esketamine nasal spray or discontinue esketamine treatment and switch to placebo nasal spray, with all patients in both treatment groups continuing oral antidepressant treatment. In SUSTAIN-1, among those who had achieved stable remission, 39 (45.3%) patients in the antidepressant plus placebo group experienced a relapse event during the maintenance phase (Daly *et al*., 2019). This observation is in line with relapse rates seen in the STAR*D study in levels 3 and 4 (Rush *et al*., 2006), respectively, where relapse rates in those achieving remission following the 12- to 14-week acute treatment phase were 42.9 and 50.0% with mean times to relapse of 3.9 and 2.5 months, respectively, even while continuing the treatment to which they had responded. Thus, in patients with TRD, the relapse rates observed after cessation of esketamine and continuation on antidepressant plus placebo resemble those reported during maintenance treatment with an oral antidepressant alone.

Dr Gastaldon and associates argue that the Risk Evaluation and Mitigation Strategy (REMS) in place for esketamine 'implies approval without knowledge of the potential negative consequences of esketamine prescribing.' Such is not the case. The safety profile of esketamine was well characterized in the clinical development programme that included 19 phase 1 studies, four phase 2 studies and six phase 3 studies in TRD. At the time the NDA was written, a total of 1708 participants with TRD had received at least one dose of esketamine in six completed phase 2 and 3 studies (Food and Drug Administration, 2019). Similar to numerous approved treatments (e.g. clozapine) (Food and Drug Administration, 2020), the REMS programme for esketamine nasal spray was introduced to reinforce behaviours/actions that support the safe use of medications, thereby helping to ensure that benefits outweigh risks. Specifically, the intent of the REMS is to mitigate the risk of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, while providing access to appropriate patients with TRD in need of treatment (Kim *et al*., 2019).

Gastaldon and co-authors also incorrectly stated in their Commentary that ' six suicides happened and all of them were in the esketamine arm'. To clarify, seven deaths were reported in the entire esketamine development programme for TRD as of 31 December 2018 (combined cumulative exposure 1812 patient-years), three from completed suicide (all in open-label study/study phases with no control group). On the basis of these three events, the completed suicide rate in the esketamine development programme for TRD is 0.17 per 100 patient-years (95% CI 0.04–0.45), which is not greater than the completed suicide rate of 0.47 per 100 patient-years of treatment reported in a meta-analysis of 30 TRD studies that included over 15 000 patients with TRD (Bergfeld *et al*., 2018). Of the four additional deaths reported, none was considered by the investigator to be related to esketamine.

In conclusion, the sponsor sought agreement from health authorities, including FDA and CHMP, to design a comprehensive clinical trial programme to establish efficacy and safety in patients with TRD and comply with regulatory guidelines. The FDA and CHMP approved the application based on consistent efficacy of esketamine and evidence supporting long-term safety (Kim *et al*., 2019; European Medicines Agency, 2019*a*). Overall, the programme provides substantial evidence that esketamine nasal spray plus oral antidepressant acts rapidly (Spravato™ 2019; European Medicines Agency, 2019*b*), shows robust efficacy in TRD and maintains this benefit over time (Daly *et al*., 2019).

Acknowledgements. We acknowledge Sandra Norris, PharmD of the Norris Communications Group LLC, supported by Janssen Research and

https://doi.org/10.1017/S2045796020000268 Published online by Cambridge University Press

Development, LLC, for medical writing assistance and Ellen Baum, PhD (Janssen Global Services, LLC) for additional editorial support.

Author contributions. MM, EJD, VP, KH, CC and WCD contributed equally to this Comment, including writing and approval of the text for submission.

Conflict of interest. MM, EJD, VP, KH, CC and WCD are employees of Janssen Research & Development, LLC and are stockholders of Johnson & Johnson, Inc.

References

Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A and Denys D (2018) Treatment-resistant depression and suicidality. *Journal of Affective Disorders* **235**, 362–367.

Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H and Drevets WC (2018) Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* **75**, 139–148.

Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, Lane R, Lim P, Duca AR, Hough D, Thase ME, Zajecka J, Winokur A, Divacka I, Fagiolini A, Cubala WJ, Bitter I, Blier P, Shelton RC, Molero P, Manji H, Drevets WC and Singh JB (2019) Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* **76**, 893–903.

European Medicines Agency (2010) Guideline on clinical investigation of medicinal products in the treatment of depression. EMA/CHMP/185423/2010 Rev. 2. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression_en.pdf (Accessed 28 January 2020).

European Medicines Agency (2019*a*) Spravato EPAR. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/spravato (Accessed 28 January 2020).

European Medicines Agency (2019*b*) Spravato (esketamine) summary of product characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf (Accessed 28 January 2020).

Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, Vitagliano D, Blier P, Fava M, Liebowitz M, Ravindran A, Gaillard R, Ameele HVD, Preskorn S, Manji H, Hough D, Drevets WC and Singh JB (2019) 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* **22**, 616–630.

Food and Drug Administration (2019) Drug approval package: Spravato. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000TOC.cfm (Accessed 28 January 2020).

Food and Drug Administration (2020) Approved risk evaluation and mitigation strategies (REMS). Available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (Accessed 28 January 2020).

Gastaldon C, Papola D, Ostuzzi G and Barbui C (2020) Esketamine for treatment resistant depression: a trick of smoke and mirrors? *Epidemiology and Psychiatric Sciences* **29**, e79, 1–4. https://doi.org/10.1017/S2045796019000751.

Kim J, Farchione T, Potter A, Chen Q and Temple R (2019) Esketamine for treatment-resistant depression – first FDA-approved antidepressant in a new class. *New England Journal of Medicine* **381**, 1–4.

Melander H, Salmonson T, Abadie E and van Zwieten-Boot B (2008) A regulatory Apologia – a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *European Neuropsychopharmacology* **18**, 623–627.

Montgomery SA and Möller HJ (2009) Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? *International Clinical Psychopharmacology* **24**, 111–118.

Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, Hough D, Manji H, Drevets WC, Sanacora G, Steffens DC, Adler C, McShane R, Gaillard R, Wilkinson ST and Singh JB (2020) Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression – TRANSFORM-3. *American Journal of Geriatric Psychiatry* **28**, 121–141.

Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, Mazzucco C, Hough D, Thase ME, Shelton RC, Molero P, Vieta E, Bajbouj M, Manji H, Drevets WC and Singh JB (2019) 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. *American Journal of Psychiatry* **176**, 428–438.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J and Fava M (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *American Journal of Psychiatry* **163**, 1905–1917.

Spravato™ (2019) (Esketamine) nasal spray prescribing information. © 2019 Janssen Pharmaceutical Companies.

US Department of Health and Human Services, Food and Drug Administration (2018) Major depressive disorder: developing drugs for treatment. Guidance for industry. Draft June 2018. Available at https://www.fda.gov/media/113988/download (Accessed 28 January 2020).

Wajs E, Aluisio L, Holder R, Daly E, Lane R, Lim P, George JE, Morrison R, Sanacora G, Young AH, Kasper S, Sulaiman AH, Li C-T, Paik J-W, Manji H, Hough D, Grunfeld J, Jeon HJ, Wilkinson ST, Drevets WC and Singh JB (2020) Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *Journal of Clinical Psychiatry* **81**, 19m12891.