Letter to L. Annemans, Senior Editor of the Journal

Expert Review of Pharmacoeconomics & Outcomes Research

Dear L. Annemans,

We read with interest the paper entitled "Cognitive behavior therapy for health anxiety: systematic review and meta-analysis of clinical efficacy and health economic outcomes" by Axelsson & Lagerlof [1], published in your Journal on the 20th of December 2019. The authors conducted a systematic review and meta-analysis of 19 randomized controlled trials of patients with health anxiety and found the pooled effect size of cognitive behavioural therapy (CBT) to be of moderate to large magnitude (g=0.79 95% CI 0.57–1.01). The authors concluded that "two-thirds of patients respond to treatment and about half are in remission post-treatment" and stated that "CBT is highly effective for health anxiety and probably cost-effective in comparison to both active and passive controls".

This is an important and timely clinical issue given that hypochondriasis was recently reclassified by both the ICD-11 (among the Obsessive Compulsive or Related Disorders) and the DSM-5 (termed illness anxiety disorder, among the Somatic Symptom Related Disorders) and the condition and its treatment are coming under greater scrutiny by mental health professionals. The authors draw some strong conclusions about the efficacy of CBT for health anxiety; however, we would like to raise some points that contextualise such conclusions.

One notable feature of the 19 studies making up the meta-analysis is that almost half (k=9) used waiting-list as the control comparator. Indeed, the authors reported that 'control condition' was a significant moderator of effect size (p=0.032). In particular, the effect size reduced from *g* = 1.08 (95% CI 0.86-1.30), I^2 = 44% for CBT vs. waiting list (k=14) to *g* = 0.64 (95% CI 0.06-1.23), I^2 = 84% for CBT versus a psychological comparator (k= 5) and even further to *g* = 0.54 (95% CI 0.29-0.79), I^2 = 60% for studies comparing CBT versus 'treatment as usual' (k= 4). These findings suggest a more modest effect for CBT than the authors affirm. The numbers of trials are of course smaller in each of the other control comparisons, so we re-ran the analyses after excluding the 14 wait-list comparisons. The new effect size, derived from studies comparing CBT to psychological control (k=5), attention control (k=1) , antidepressant (k=2), pill placebo (k=2) and treatment as usual (k=4), was significantly smaller than the effect reported by Axelsson & Lagerlof: Hedge's *g* = 0.51 (95% CI

0.16-0.86), I^2 = 84.75%; and this accords with the well-documented effect-size inflation often associated with using wait-list controls [2-4].

This inflation is evident at the level of individual studies through the presence of apparent nocebo effects. For example, in the Bovell et al. study [5] (which seems to be an unpublished thesis), CBT produced an extremely large effect size of *d* = 2.43, which partly reflects a large deterioration in the waiting list control, whose symptom ratings worsened during the trial - for the treatment group, Short Health Anxiety Inventory (SHAI) scores improved from 33.5 (6.10) to 21.7 (7.33), while the wait-list deteriorated from 29 (9.42) to 38 (6.00). The striking difference in effect sizes between trials using wait-list controls and those using an - arguably fairer - control comparator is crucial for interpreting the efficacy of interventions. Not least of all, any effect size inflation is likely to lead to future underpowering of trials. Even assuming a modest effect size reduction from 0.79 (all trials) to 0.51 (minus wait-list), this will result in a difference in power from less than 30 per group to over 60 per group. As the authors had set-out to test whether the choice of control condition acted as a moderator of the effect size of CBT, we were surprised that this was not commented on further in the paper. Moreover, it is noteworthy that the antidepressant comparator (2 studies), as graphically shown in the forest plot, is either statistically superior or equal to CBT, and that CBT did not show superior efficacy to pill placebo (2 studies).

The high level of heterogeneity among the findings also deserves closer scrutiny (I^2 ranged from 44% for comparisons against waiting list to 84% for comparisons against psychological control) and suggests a considerable degree of unreliability in the effect size. We appreciate this may have resulted from a combination of many methodological factors, including the profound between-study variability in choice of control and/or the different inclusion criteria used to define the study samples (e.g. in most of the studies the condition investigated is hypochondriasis, while in others health anxiety [6]). Health anxiety is a more common condition and incorporates a broader patient group with symptoms much milder than those identified associated with ICD hypochondriasis (or DSM-5 illness anxiety disorder), which is a chronic, highly distressing and disabling disorder and which may respond quite differently to the same interventions. Interestingly, two out of the four studies with the largest effect sizes (1.00+) [6,7] did not address specifically hypochondriasis or illness anxiety disorder (but investigated health anxiety as a broad spectrum or also included somatic symptom disorder). Arguably a meta-analysis selecting studies by applying standardised and stricter

entry criteria focussed on a diagnosis of hypochondriasis or equivalent would produce a different and potentially more reliable result.

Finally, the lack of preregistration for the meta-analysis also leaves it open to criticism of selecting post hoc outcomes and consequently increased risk of bias. For example, the methodology appears to prioritise outcomes measured on the Short Health Anxiety Inventory (SHAI) over those derived on Whiteley Index (WI). However, it can be seen that the authors were inconsistent on this point and in some studies where both the SHAI and Whitely were available [8-10] they chose differently and used the scale that reported the larger CBT-related improvement.

We contend this meta-analysis demonstrates that CBT may have a modest effect on reducing symptoms of health anxiety but this conclusion is unreliable and does not necessarily extrapolate to the more serious clinical disorder of hypochondriasis.

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Sincerely,

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Disclosure of competing interests:

Prof. Naomi A. Fineberg declares that in the past 3 years she has held research or networking grants from the ECNP, UK NIHR, EU H2020, MRC, University of Hertfordshire; she has accepted travel and/or hospitality expenses from the BAP, ECNP, RCPsych, CINP, International Forum of Mood and Anxiety Disorders, World Psychiatric Association, Indian Association for Biological Psychiatry, Sun; she has received payment from Taylor and Francis and Elsevier for editorial duties. In the past 3 years, she has accepted a paid speaking engagement in a webinar sponsored by Abbott. Previously, she has accepted paid speaking engagements in various industry supported symposia and has recruited patients for various industry-sponsored studies in the field of OCD treatment. She leads an NHS treatment service for OCD. She holds Board membership for various registered charities linked to OCD. She gives expert advice on psychopharmacology to the UK MHRA.

Prof. Umberto Albert declares that in the past 3 years has been a consultant and/or a speaker for Angelini, Neuraxpharm, Janssen Cilag, Lundbeck, Innova Pharma.

Prof. Keith Laws, Dr. Luca Pellegrini and Dr. Jemma Reid report no financial relationships with commercial interests.