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Commentary on the article: "Maintenance of wellness in patients with obsessive-compulsive disorder who discontinue medication after exposure/response prevention augmentation A randomized clinical trial" Foa EB et al., JAMA Psychiatry. 2022;79(3):193–200 (1)

We read this paper, recently published in the Journal of the American Medical Association [1], with great interest, and as OCD specialists at four centers in the UK and US, we wish to comment collectively on specific issues raised by the article, which we judge have important public health implications.

The authors report a moderate sized study of patients with OCD receiving selective serotonin reuptake inhibitors (SSRI) and cognitive behavior therapy (CBT) with exposure and response prevention (EX/RP) who have entered symptom remission. They compare outcomes in those for whom SSRI is tapered and withdrawn ($n = 51$) versus those remaining on SSRI ($n = 50$). Over six months, mean Y-BOCS, Hamilton Depression Rating scale (HDRS) and Quality-of-Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF) scores in the two groups numerically worsen only a little from baseline and remain comparable (mean within-person change, Y-BOCS $\leq$2.33 points; HDRS $\leq$2.08 points; Q-LES-Q-SF $\leq -5.23\%$), though 'clinical worsening' (operationalized as a score of much worse or very much worse on the Clinical Global Impression Improvement scale for 2 consecutive weeks) was significantly higher ($p < .04$) in the SSRI-withdrawal group. Indeed, SSRI discontinuation was associated with almost double the risk of a major clinical deterioration, as compared to SSRI continuation (45.1% vs 24.0%). The authors interpret this finding as evidence that 'after successful SRI augmentation with EX/RP, patients who achieve wellness after EX/RP could, on average, discontinue their SRI with noninferior outcomes on measures of OCD, depression, and quality of life compared with those who continued their SRI', and further 'Patients with OCD who achieve wellness after EX/RP therapy may be able to discontinue their SRI with noninferior outcomes compared with those who continue their SRI, but careful monitoring is needed.' [1].

Readers might conclude from the framing of the findings that giving EX/RP will allow clinicians to discontinue SSRIs safely in many cases, as long as careful monitoring is provided. This is a strong position (particularly in light of the authors' finding that 45% of those who tapered SSRIs demonstrated clinical worsening) and may have untoward consequences for some patients or clinicians, who could see this as a 'green light' to discontinue medication without appropriate consideration of the high risk of relapse (and other risks and harms). Such a position would, in our view, require compelling evidence, considering a) that relapse in OCD has overwhelmingly negative consequences for patients in terms of quality of life [2] and thus should be avoided; and b) the weight of evidence to the contrary.

Large-scale relapse prevention studies and meta-analyses have shown that discontinuing SSRI is a causal factor for relapse of OCD, in terms of speed of relapse and/or proportion of patients relapsing [3]. Moreover, one meta-analysis included a sensitivity analysis, which showed that giving CBT in acute treatment did not protect against relapse following drug discontinuation in a range of anxiety and related disorders including OCD and PTSD [4]. Of note, whereas three OCD relapse prevention studies did not show a significant advantage of remaining on SSRI on the primary analysis (thought to be related to methodological issues including inadequate duration of follow-up or use of an unduly stringent relapse criterion), clinical worsening was seen on secondary outcomes in those patients switched to placebo. In addition, whereas fluoxetine was not efficacious in preventing relapse when the data for all dosages were pooled, analysis of the maximum (60 mg) dose showed efficacy, highlighting the importance of sustained treatment with SSRI at high doses for relapse prevention in OCD.

We highlight the wealth of prior research data relating to the risks associated with relapse and the importance of protecting patients against relapse, since this was not fully addressed by the authors in their paper. Further, attention to this literature may have led the authors to a very different study design and different conclusions, as described below.

There is a problem in the way the discontinuation phase is *designed*. The authors state they are interested in finding out what happens to patient wellness 'after EXP/RP'. Most relapse prevention studies examine outcomes of patients for at least six months after treatment is fully discontinued and tend to show that relapses in OCD gradually accrue over time. Therefore, the longer the period off-treatment, the greater the differential risk of relapse. In this study, patients continued frequent sessions with their therapist and doctor throughout the discontinuation phase. In the cases of therapist sessions, activities included the following: "*During the taper phase, fortnightly meetings with a psychiatrist for 30 minutes and a therapist for 45 minutes, on alternate weeks. During the maintenance phase, monthly meetings with their psychiatrist (30 minutes) and the therapist (45 minutes). During these sessions, the psychiatrist reviewed medication adherence and adverse effects; the therapist reviewed the use of EX/RP therapy in daily life.*". All this therapeutic activity occurred during the period when SSRI had stopped and amounts, in our opinion, to ongoing EX/RP, albeit in a less intensive form. This ongoing therapy is likely to have reduced chances of relapse in both groups and may therefore account for the finding that both groups remained (on average) well and showed little symptomatic difference over this period. We believe the study shows no period of true treatment discontinuation. Instead, what the authors seem to show is the following: if CBT sessions are continued albeit at lower density, well-being can be sustained on one measure, but with almost double the rate of clinically significant deterioration compared to continuing SSRI. We cannot tell what would have happened if CBT was stopped for a sustained period, but prior data suggest high rates of relapse would be

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expected [4].

The analysis is also unusual as it focuses on the Y-BOCS score (which is a continuous variable representing OCD symptom severity) as the primary outcome, and not on a categorical variable (i.e., a relapse measure). The authors refer to the Y-BOCS as a measure of wellness - which could be mistakenly interpreted as wellbeing - and although they measure QoL, this is downgraded and analyzed as a secondary outcome. Most relapse prevention studies evaluate some form of categorical outcome (i.e., relapse from remission into illness state) as the primary measure since this is a major concern for patients. Many recognized definitions of OCD relapse exist [3], which the authors have not adequately referenced. However, 'clinical worsening' was analyzed in this study, albeit as an 'exploratory measure' and may be interpreted as a proxy measure of OCD relapse. We note the significantly greater rate of clinical worsening seen after SSRI discontinuation, which we believe requires much stronger emphasizing in the interpretation of these findings.

We also note that the authors did not measure adverse events occurring due to psychotherapy. In a previous study, 14.1% of people who had received psychological treatment for anxiety and/or depression in usual healthcare settings reported they had experienced lasting negative effects of this treatment [5]. All clinical trials should measure adverse events and report them. In the case of this study, patients with adverse events due to psychotherapy would not qualify as having achieved wellness prior to discontinuation of EX/RP. Therefore, conclusions regarding wellness are difficult to defend with certainty.

From a clinical perspective, the conclusions drawn by the authors are potentially hazardous. In our clinical experience, one of the greatest challenges in the treatment of OCD is to support a patient who has achieved improvement or remission to remain on that same dose of SSRI to prevent relapse. To overturn established relapse-prevention practice based on existing evidence (including evidence from high quality meta-analysis) and instead adopt a practice of giving CBT in order to remove SSRI, would require a much stronger evidence base than this study provides. Moreover, cost-effectiveness may be a concern as providing regular psychotherapy over the long-term is not currently feasible in many healthcare systems.

Conflict of interest

Prof. Fineberg in the past three years has received research funding paid to her institution from the National Institute for Health Research, COST Action and Orchard. She has received payment for lectures on psychiatric diagnosis from the Global Mental Health Academy and for expert advisory work on psychopharmacology from the Medicines and Healthcare Products Regulatory Agency, publishing royalties from Oxford University Press and an honorarium from Elsevier for editorial work. She is Editor in Chief, Comprehensive Psychiatry. She has received financial support to attend meetings from the British Association for Psychopharmacology, European College for Neuropsychopharmacology (ECNP), Royal College of Psychiatrists, International College for Neuropsychopharmacology, COST, World Psychiatric Association, International Forum for Mood and Anxiety Disorders, American College for Neuropsychopharmacology. In the past she has received funding from various pharmaceutical companies for research into the role of SSRIs and other forms of medication as treatments for OCD and for giving lectures and attending scientific meetings.

Prof. Hollander has received research grants from Department of Defense, Orphan Products Division of Food and Drug Administration, Hoffman La Roche, GW, and honoraria from Elsevier for Editorial work.

Prof. Baldwin receives a personal honorarium from Wiley for editorial work for *Human Psychopharmacology*. In the last three years he has received research funding paid to his institution from Health Education England, the National Institute for Health Research, and the Medical Research Council.

Prof. Grant has received research grants from Otsuka and Biohaven Pharmaceuticals. He receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies and has received royalties from Oxford University Press, American Psychiatric Publishing, Inc., Norton Press, and McGraw Hill.

Prof. Laws, Dr. Drummond, Dr. Pellegrini, Dr. Reid, Dr. Wellsted and Dr. Nezgovorova have no conflict to declare.

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