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Invited Letter Rejoinder

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PRINCE Secondary: transdiagnostic cognitive behaviour therapy for persistent physical symptoms

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Dear Professor Kendler and Professor Murray

Persistent physical symptoms (PPS) are associated with distress, disability, and high costs within the working population (Bermingham, Cohen, Hague, & Parsonage, 2010). We developed an approach to treating such symptoms which target overlapping psychological and behavioural responses called transdiagnostic cognitive behaviour therapy (TDT-CBT) (Chalder & Willis, 2017). We compared therapist delivered TDT-CBT plus treatment as usual (TAU) with TAU alone for patients with PPS in a randomised controlled trial. We tested the efficacy and cost effectiveness. We found no difference on our primary outcome, which was the Work and Social Adjustment Scale (WASAS) at 52 weeks. However, relevant secondary outcomes, including severity of symptoms and clinical global impression, had a treatment effect in favour of TDT-CBT at 12 months. The statistical analysis was described in the protocol (Chalder et al., 2019) statistical analysis plan (SAP) and outcome paper (Chalder et al., 2021). In brief, separate regressions were done for each outcome and we used multiple imputation by chained equations (MICE) including measures of the outcome at all time points including end of treatment.

Tack and Tuller (2021) take issue with our interpretation of the results, the fact that we reported change on the WASAS at 20 weeks which marked the end of treatment, lack of adjustment for multiple comparisons, reliance on subjective outcomes and the fact that we did not control for therapist time and attention, all issues highlighted in either the published protocol, SAP, or main paper.

We stated in the protocol that the models used to assess the primary outcome would contain all four follow-up time points as the dependent variables. This included the WASAS at 20 weeks. The analysis models and secondary objectives were also discussed in detail in the SAP which was agreed and signed off prior to analysis. These objectives were clearly stated and included the WASAS at all post randomisation follow-up time points. It has been suggested that there is no need to adjust for multiplicity if the primary outcome is pre-specified, as the secondary outcomes are seen as subsidiary and exploratory (Li et al., 2017). Although exploratory, we did use a method for adjusting for multiplicity and under the Benjamini–Hochberg procedure all highlighted secondary outcomes would still be considered discoveries. Although change was small on the secondary outcomes, all changes were in the same direction which indicated that the approach may have been having some effect. The number of sessions provided in treatment was relatively small and may explain the lack of clinical effectiveness. We do not agree that we overstated the findings. The abstract states that TDT-CBT may be helpful for people with a range of PPS and that further work is needed to maintain or maximise effects. The papers conclusions state '*Our transdiagnostic model and treatment of PPS was not superior to treatment as usual at the final follow-up (52 weeks)*' (Chalder et al., 2021). Knowledge gained from this preliminary trial will influence the planning of future studies which may control for therapist time and attention.

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