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The efficacy of complicated grief therapy for DSM-5-TR prolonged grief disorder

The American Psychiatric Association recently announced the inclusion in the DSM-5-TR of a new category for prolonged grief disorder (PGD)[1,2], following introduction of this category in the ICD-11. Our group previously demonstrated the efficacy of a targeted treatment (complicated grief therapy, CGT) for complicated grief, a condition corresponding in many respects to PGD. We examined now the performance of that treatment among people who met the DSM-5-TR criteria for PGD.

CGT is a manualized 16-session intervention developed when we observed that treatments for depression did not appear to be effective for complicated grief[3]. We considered loss of a loved one to be a major life stressor[4] and understood grief from an attachment theory perspective[5]. We conceptualized grief after attachment loss as typically emerging in an acute form and becoming integrated over time as the reality of the loss is accepted and the capacity for well-being is restored. We understood complicated grief as a condition in which the initial intense form of grief persisted and interfered with functioning. A body of research informed our understanding of impediments to adapting to the loss. We developed a treatment that focused on facilitating adaptation to loss and addressing impediments, drawing upon strategies and techniques from prolonged exposure, motivational interviewing, positive psychology, interpersonal psychotherapy, and psychodynamic psychotherapy.

CGT was tested in three randomized controlled trials funded by the US National Institute of Mental Health[6-8]. For the present report, we analyzed data from one of these trials[6], in which participants (N=395) were people with a score of 30 or higher on the Inventory of Complicated Grief (ICG) who underwent a clinical interview confirming that grief was the primary problem. People with current substance use disorder, or a lifetime history of psychotic disorder, bipolar I disorder, active suicidal plans requiring hospitalization, or a Montreal Cognitive Assessment score less than 21 were excluded.

These patients were evaluated through the Structured Clinical Interview for Complicated Grief (SCI-CG), an instrument that can be used to identify DSM-5-TR criteria for PGD[9]. The evaluation was available for 307 study participants, 77 (25.1%) of whom were bereaved between 6 and 12 months and therefore did not meet the DSM-5-TR criteria solely due to time considerations. Of the remaining 230, 194 (84.3%) met DSM-5-TR criteria for PGD and 36 (15.7%) did not. All patients recruited for the parent study were randomized either to citalopram or to placebo, with or without CGT[6].

Among patients meeting criteria for PGD (N=194), we compared study outcomes at endpoint (week 20) for those who received CGT (N=96) versus those who did not receive it (N=98). The main outcome was treatment response measured as a rating of "much improved" or "very much improved" on the Clinical Global Impression (CGI) Improvement. We further used several grief symptom measures: the ICG, the Grief-Related Avoidance Questionnaire (GRAQ), the Typical Beliefs Questionnaire (TBQ), and the Grief-Related Work and Social Adjustment Scale (WSAS). Chi-squared tests were used for binary outcomes and two sample t-tests for continuous outcomes. All hypothesis tests were two-sided with a 5% level of significance. All analyses were performed in R (v1.4.1717). The parent study had been approved by the relevant institutional review board[6]. Written informed consent had been obtained from all participants before baseline assessment.

The sample of patients with PGD was not significantly different with respect to demographic and clinical variables from the parent study sample. Most patients were female (79.9%), white (80.9%), completed at least partial college (90.2%), and were bereaved of a parent or spouse (68.6%) by illness (65.5%) for 4-5 years on average. The sample had an average age of 52.7±14.2 years. Patients had high rates of current depression (69.6%), current post-traumatic stress disorder (46.4%), and suicidal ideation since the loss (61.9%) (see also supplementary information).

Treatment response for the sample with PGD closely reflected that of the parent study. Specifically, response rates for those randomized to CGT vs. no CGT were 88.2% vs. 60.9% ($p<0.001$) for the DSM-5-TR PGD group compared to 82.9% vs. 63.4% for all participants in the parent study. Also comparable to the parent study, average post-treatment scores on grief-related symptoms and impairment were significantly lower for those who received CGT vs. no CGT (ICG: 17.7 vs. 25.4, $p<0.001$; WSAS: 7.9 vs. 13.4, $p=0.001$; GRAQ: 9.4 vs. 14.6, $p=0.01$; TBQ: 3.9 vs. 7.1, $p<0.001$) (see also supplementary information).

Our results indicate that study participants who met DSM-5-TR criteria for PGD showed no significant demographic or clinical differences from the full parent study sample. Those diagnosed with PGD showed significantly greater response rates to CGT vs. no CGT, with results nearly identical to the parent study.

These findings are limited by the need to apply retrospectively the DSM-5-TR criteria for PGD, and diagnosis may have been less accurate than if made using a validated instrument[1]. Additionally, those diagnosed with PGD for these analyses represented only

half of the originally randomized sample. However, almost half (43.8%) of the omitted participants simply did not receive the assessment needed to diagnose PGD, and another 38% were excluded because it was too soon (six months to one year since the loss) to receive a PGD diagnosis. Further, those assessed showed no differences in demographic or clinical characteristics from participants in the parent study.

We endorse continued study of effective treatments for PGD. In the meantime, we believe that clinicians will benefit from knowing that CGT, a strongly validated intervention[6-8], can be appropriately re-labeled as prolonged grief disorder therapy (PGDT).

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Supplementary information on the study is available at http://christinemauro.com/downloads/tables_17.02.2022.pdf.

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Risk of new-onset psychiatric sequelae of COVID-19 in the early and late post-acute phase

Recent publications have documented that a proportion of COVID-19 patients develop psychiatric symptoms during or after acute infection[1]. We investigated this risk in the context of the National COVID Cohort Collaborative (N3C) – a centralized, harmonized, high-granularity electronic health record (EHR) repository[2] – using the largest retrospective cohort reported to date.

Two previous large-scale EHR studies examined psychiatric sequelae 90 and 180 days after COVID-19 diagnosis. A cohort of 44,779 individuals with COVID-19 was propensity score-matched to control cohorts with conditions such as influenza and other respiratory tract infections (RTI). In the 90 days following the initial presentation, the incidence proportion of new-onset psychiatric conditions was 5.8% in the COVID-19 group vs. 2.5% to 3.4% in the control groups[3]. A follow-up study also included individuals with a prior history of mental illness and similarly showed an increased risk of psychiatric conditions in the six months following initial presentation[4].

To validate these findings, we leveraged data from N3C, which at our cutoff date of October 20, 2021 had 1,834,913 COVID-19 positive patients and 5,006,352 comparable controls. Our data set was drawn from 51 distinct clinical organizations. We included patients in the COVID-19 cohort if they had a confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction or antigen test after January 1, 2020. Controls were selected from patients with a diagnosis of a RTI other than COVID-19. We excluded from this analysis patients with a history of any mental illness prior to 21 days after COVID-19 diagnosis, as well as patients without a medical record extending back a year prior to COVID-19. There were 245,027 COVID-19 positive individuals available for propensity matching.

Each COVID-19 patient was matched with a control patient from the same institution whose age differed by no more than 5 years. Propensity score matching was done on 34 factors using a logistic regression model including main effect terms, resulting in 46,610 matched patient pairs. Multivariable Cox regression was performed to compare the incidence of new-onset mental illness for all psychiatric conditions, mood disorders and anxiety disorders for 21 to 365 days following initial presentation. We additionally considered dyspnea as a positive control.

We tested the Cox regression proportional hazard assumption for comparisons of COVID-19 patients and controls[5]. Schoenfeld residual analysis yielded a significant p-value and led us to reject the null hypothesis of a constant proportional hazard over the full time period of 21-365 days. We therefore separated the cohort into two time intervals (before and after 120 days) in which the proportional hazard assumption was not violated.

We identified a statistically significant difference in the hazard rate of new-onset psychiatric sequelae between COVID-19 and RTI in the early post-acute phase (from 21 to 120 days), but not in the late post-acute phase (from 121 to 365 days). The estimated incidence proportion (as modeled on the log-hazard scale over time) of a new-onset psychiatric diagnosis in the early post-acute phase for the COVID-19 group was 3.8% (95% CI: 3.6-4.0), significantly higher than the 3.0% (95% CI: 2.8-3.2) for the RTI group, with a hazard ratio (HR) of 1.3 (95% CI: 1.2-1.4). The HR for new-onset mental illness in the late post-acute phase was not significant in the COVID-19 compared to the RTI group (HR: 1.0; 95% CI: 0.97-1.1).

Similar findings were obtained for anxiety disorders, but not for mood disorders. The estimated incidence proportion of a new-onset anxiety disorder diagnosis was significantly increased for COVID-19 patients (2.0%; 95% CI: 1.8-2.1) compared to RTI patients (1.6%; 95% CI: 1.5-1.7) in the early post-acute phase (HR: 1.3; 95% CI: 1.1-1.4). However, the estimated incidence proportion