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Optimizing Treatment of Complicated Grief:

A Randomized Clinical Trial

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Abstract

IMPORTANCE—To our knowledge, this is the first placebo-controlled randomized clinical trial to evaluate the efficacy of antidepressant pharmacotherapy, with and without complicated grief psychotherapy, in the treatment of complicated grief.

OBJECTIVE—To confirm the efficacy of a targeted complicated grief treatment (CGT), determine whether citalopram (CIT) enhances CGT outcome, and examine CIT efficacy without CGT.

DESIGN, SETTING, AND PARTICIPANTS—Included in the study were 395 bereaved adults who met criteria for CG recruited from March 2010 to September 2014 from academic medical centers in Boston, Massachusetts; New York, New York; Pittsburgh, Pennsylvania; and San Diego, California. Co-occurring substance abuse, psychosis, mania, and cognitive impairment were exclusionary. Study participants were randomized using site-specific permuted blocks stratified by major depression into groups prescribed CIT (n = 101), placebo (PLA; n = 99), CGT with CIT (n = 99), and CGT with PLA (n = 96). Independent evaluators conducted monthly assessments for 20 weeks. Response rates were compared under the intention-to-treat principle, including all randomized participants in a logistic regression with inverse probability weighting.

INTERVENTIONS—All participants received protocolized pharmacotherapy optimized by flexible dosing, psychoeducation, grief monitoring, and encouragement to engage in activities. Half were also randomized to receive manualized CGT in 16 concurrent weekly sessions.

MAIN OUTCOMES AND MEASURES—Complicated grief–anchored Clinical Global Impression scale measurments every 4 weeks. Response was measured as a rating of “much improved” or “very much improved.”

RESULTS—Of the 395 study participants, 308 (78.0%) were female and 325 (82.3%) were white. Participants’ response to CGT with PLA vs PLA (82.5% vs 54.8%; relative risk [RR], 1.51; 95% CI, 1.16–1.95; $P = .002$; number needed to treat [NNT], 3.6) suggested the efficacy of CGT, and the addition of CIT did not significantly improve CGT outcome (CGT with CIT vs CGT with

PLA: 83.7% vs 82.5%; RR, 1.01; 95% CI, 0.88–1.17; *P* = .84; NNT, 84). However, depressive symptoms decreased significantly more when CIT was added to treatment (CGT with CIT vs CGT with PLA: model-based adjusted mean [standard error] difference, −2.06 [1.00]; 95% CI, −4.02 to −0.11; *P* = .04). By contrast, adding CGT improved CIT outcome (CIT vs CGT with CIT: 69.3% vs 83.7%; RR, 1.21; 95% CI, 1.00–1.46; *P* = .05; NNT, 6.9). Last, participant response to CIT was not significantly different from PLA at week 12 (45.9% vs 37.9%; RR, 1.21; 95% CI, 0.82–1.81; *P* = .35; NNT, 12.4) or at week 20 (69.3% vs 54.8%; RR, 1.26; 95% CI, 0.95–1.68; *P* = .11; NNT, 6.9). Rates of suicidal ideation diminished to a substantially greater extent among participants receiving CGT than among those who did not.

CONCLUSIONS AND RELEVANCE—Complicated grief treatment is the treatment of choice for CG, and the addition of CIT optimizes the treatment of co-occurring depressive symptoms.

TRIAL REGISTRATION—clinicaltrials.gov Identifier: NCT01179568

Complicated grief (CG) is a chronic impairing condition that occurs in about 7% of bereaved people (2% to 3% of general population).[1,2] The syndrome includes persistent maladaptive thoughts, dysfunctional behaviors, and poorly regulated emotionality that interfere with adaptation after loss.[3] Although co-occurring depressive symptoms are common, CG can be clearly differentiated from major depression both in its primary symptomatology[4] and response to treatment.[5,6] Core symptoms of yearning and sorrow, preoccupying thoughts of the deceased, and difficulty accepting the painful reality of the death are different from persistent depressed mood, anhedonia, worthlessness, and psychomotor and neurovegetative symptoms, which are the hallmarks of depression. Studies[5,6] document a significantly better response to complicated grief treatment (CGT) than interpersonal psychotherapy, which has well-documented efficacy for depression.[3]

Provisional guidelines and criteria for diagnosis have been proposed for the *International Statistical Classification of Diseases, Eleventh Revision*[3] and *DSM-5*.[7] Until these are approved, patients can be reliably identified by a screening questionnaire[8] and a semistructured clinical interview.[9] Chronic high levels of distress and impairment and increased risk for suicide, cancer, and cardiovascular disease constitute a strong indication for treatment. We developed CGT to target adaptation to loss and found it produced a better outcome than grief-focused interpersonal psychotherapy[5,6]; individuals in our psychotherapy trial who were taking antidepressant medication had a markedly higher treatment completion rate. In addition, antidepressant medications can decrease the intensity of emotions and somatic symptoms and improve cognitive functioning, and there are some pilot data suggesting that antidepressant medication can be helpful for people with CG.[10–12] However, to our knowledge, there are no randomized clinical studies testing whether antidepressants enhance CGT efficacy or whether they are efficacious without CGT.[13] We conducted a randomized clinical trial to test the hypothesis that citalopram (CIT) would be superior to pill placebo (PLA) with and without CGT. Our data provide important information for evidence-informed clinical care and shared decision-making in specialty mental health and other health care settings.

Methods

Study Design

We conducted a double-blinded, PLA-controlled trial at 4 collaborating sites (New York, New York, which was the coordinating center; Boston, Massachusetts; Pittsburgh, Pennsylvania; and San Diego, California) funded independently by the National Institute of Mental Health. Aim 1 compared CIT with PLA when administered without CGT for 12 weeks (we moved aim 1 from week 16 to week 12 in consultation with our data and safety monitoring board after a US Food and Drug Administration ruling limited the maximum dose of CIT to 40 mg daily in 2011). Aim 2 compared CIT with PLA when administered with CGT. Aim 3 examined whether adding CGT to CIT or PLA significantly improved outcomes at 20 weeks. The institutional review boards at each site approved the study; oversight was provided by an independent data and safety monitoring board. The full study protocol can be found in Supplement 1. Written informed consent was obtained from all participants before baseline assessment. Following a telephone screen (verbal consent) and in-person assessment, eligible participants were randomly assigned via a 2 × 2 factorial design to receive CIT or PLA with or without concomitant psychotherapy. All study participants received a medication prescription (CIT or PLA) from a pharmacotherapist who provided empathic support, psychoeducation, and encouragement to re-engage in activities along with monitoring and adjustment of the medication. Half also received CGT, a targeted psychotherapy entailing 16 sessions over a maximum of 20 weeks.[5,6] Our main outcome was rate of response defined as 1 (“very much improved”) or 2 (“much improved”) on the CG-anchored Clinical Global Impression Scale[14] (Table 1) as determined by independent evaluators, trained to achieve reliability on key rating instruments (treatment response κ, 0.89; 95% CI, 0.73–1.00) and blind to treatment assignment.

Recruitment

Between March 2010 and September 2014, 395 bereaved individuals aged 18 to 95 years were recruited using professional and public outreach and print, broadcast, and internet media. Referrals were made by health care professionals, bereavement counselors, and patients or family members.

Inclusion and Exclusion Criteria

Participants who scored 30 or greater on the Inventory of Complicated Grief (ICG)[8] underwent a clinical interview to confirm the presence and primacy of CG. Those with a current substance use disorder (past 6 months), a lifetime history of psychotic disorder, bipolar I disorder, active suicidal plans requiring hospitalization, a Montreal Cognitive Assessment score less than 21, or a pending lawsuit or disability claim related to the death as well as those undergoing concurrent psychotherapy or treatment with an antidepressant were excluded.

Assessment Procedures

Independent evaluators completed the Structured Clinical Interview for *DSM-IV* Axis I,[15] a supplemental interview for CG,[9] the Columbia Suicide Scale[16] modified for bereavement,

and the Clinical Global Impression Scale[14] for CG-anchored severity and improvement (Table 1). Follow-up assessments were conducted 4, 8, 12, 16, and 20 weeks after the first treatment visit and 6 months after study treatment termination. Study participants were instructed not to tell independent evaluators if they received CGT. Assessments were audiotaped; 10% were randomly selected and corated for reliability. Biweekly cross-site meetings reviewed rating procedures and included practice coratings to prevent drift.

Participants completed self-report questionnaires for secondary outcome measures of grief-related symptoms(ICG),[8] impairment (Work and Social Adjustment Scale [WSAS]),[17,18] avoidance (Grief-Related Avoidance Questionnaire [GRAQ]),[19] depressive symptoms(Quick Inventory of Depressive Symptoms–Self-report [QIDS-SR_{16}]),[20] and suicidal ideation (Columbia Suicide Scale).[16]

Pharmacotherapy

Citalopram or PLA was provided in double-blind fashion to all participants. Given participants' high levels of distress and impairment and inclusion of a PLA-only cell, our manualized pharmacotherapy approach included procedures designed to optimize participant safety and pharmacotherapy effectiveness. Prescribing clinicians received standardized site-based training and supervision. The first visit (about 45 minutes) included a focused psychosocial history and review of symptoms as well as psychoeducation using the same model as in CGT, with a rationale for using antidepressant medication. Subsequent visits (weekly for 4 weeks, biweekly for 4 weeks, and monthly thereafter) were 20 to 30 minutes. Pharmacotherapists monitored grief symptoms and provided CGT-informed clinical management that included encouragement and support for resuming normal life activities as a test of medication effectiveness. They also assessed depressive symptoms, suicidal thinking, medication adherence, and adverse effects. Specific interventions, such as exposure instructions, emotion regulation strategies, or cognitive reframing, were proscribed (specific exposure procedures and other CG-targeted psychotherapy procedures were prohibited). Medication was flexibly dosed to the maximum allowable. Supplementary visits were provided if there was a change in dosage or when it was deemed clinically indicated (eg, to follow-up on suicidal ideation). Study medication was discontinued and open treatment provided when exit criteria were met or when pharmacotherapists judged it was clinically indicated. Participants also interacted with warm, supportive, CGT-informed administrative staff. The mean (SD) dose of CIT (aim 1, week 12) was 33.9 (15.0) mg per day. The median dose was 40 mg per day.

Complicated Grief Treatment

Complicated grief treatment was delivered as in prior studies[5,6] using a manualized, well-specified 16-session protocol. Briefly, sessions 1 through 3 included history taking (relationship history and bereavement experience), the beginning of daily grief-monitoring, psychoeducation about CG and CGT, the introduction of ongoing aspirational goals work, and a conjoint session with a significant other. Sessions 4 through 9 included imaginal and situational revisiting procedures and work with memories and pictures. Session 10 was a midcourse review, followed by sessions 11 through 16, which included an imaginal conversation with the deceased. The entire study treatment manual is available at http://

www.complicatedgrief.columbia.edu/. Therapists were trained by participating in a didactic seminar and successfully completed at least 2 training cases before seeing study participants under independent site-based supervision.

Randomization

Study participants were randomized with equal probability (25%) to each treatment arm, using permuted-block randomization (block size of 4 or 8) stratified by site and by presence or absence of current major depressive disorder (MDD). Medication allocation was concealed from all study staff. Independent evaluators were blind to psychotherapy allocation.

Statistical Analysis

The range and distribution of all key demographic and clinical variables at baseline were compared across study arms by χ^2 tests or analyses of variance. Our prespecified primary analysis was cross-sectional, comparing treatment response rates for CIT vs PLA at week 12 (aim 1), for CIT with CGT vs PLA with CGT at week 20 (aim 2), and for CIT with CGT vs CIT at week 20 (aim 3) based on the intention-to-treat principle including all randomized participants. A weighted logistic regression controlled for randomization stratification variables (ie, site and baseline MDD) and race/ethnicity. Inverse probability weighting, a standard strategy to account for missing assessment data,[21–24] provided weights in the model (eAppendix 1 in Supplement 2). Our enrollment target of 440 participants lost 10% to follow-up and had a power of 76% to 83% to detect predicted between-group difference in response based on data from our 2005 study[5,11] (CGT with PLA, 40%; CGT with CIT, 60%; CIT, 40%; and PLA, 20%). All *P* values were 2-tailed, and statistical significance was defined as $P < .05$. Data were analyzed using SAS version 9.3 (SAS Institute).[25]

As with prespecified sensitivity analyses, unweighted analyses of assessment completers and longitudinal analyses using generalized linear mixed effects model with participant-specific random intercepts of the primary outcome were performed for each aim. We calculated number needed to treat (NNT) as the reciprocal of response rate. Preplanned moderator analyses examined treatment by MDD interaction (eAppendix 2 in Supplement 2) and treatment effect heterogeneity across sites.

Prespecified secondary analyses of self-report ratings of CG symptoms (ICG),[8] grief-related functional impairment (WSAS)[17,18] and avoidance (GRAQ)[19] and of depressive symptoms (QIDS-SR_{16})[20] compared changes in scores using a weighted linear regression using inverse probability weighting to adjust for missing assessments. As with sensitivity analyses, longitudinal mixed effects models with participant-specific random intercepts used all available longitudinal assessments to estimate the adjusted mean difference in week 12 and week 20 self-report outcomes (eAppendix 3 in Supplement 2). Suicidal ideation, a binary outcome derived from Columbia Suicide Scale question 1c,[16] was analyzed the same way as treatment response.

Results

Sample Recruitment and Retention

Figure 1, the study CONSORT flowchart, outlines screening, assessment, and study completion rates.

Baseline Sample Characteristics

Baseline sample characteristics are summarized in Table 2. The sample was predominantly white (325 of 395 [82.3%]), female (308 [78.0%]), and highly educated (350 [88.6%]), with slightly more than half (211 [53.4%]) completing college. The median (range) time since the loss was 2.3 (0.5–58.7) years. Most deaths were from natural causes. Two-thirds (262 [66.3%]) of the sample met criteria for current major depression. More than half (221 [55.9%]) reported a wish to be dead since the loss.

Main Outcome Analyses

Analyses suggested a greater response to CGT with PLA than PLA (82.5% vs 54.8%; relative risk [RR], 1.51; 95% CI, 1.16–1.95; $P = .002$; NNT, 3.6). Contrary to our expectation, we could not show that the addition of CIT significantly improved CGT outcome (CGT with CIT vs CGT with PLA: 83.7% vs 82.5%; RR, 1.01; 95% CI, 0.88–1.17; $P = .84$; NNT, 84). On the other hand, adding CGT did improve CIT outcome (CIT vs CGT with CIT: 69.3% vs 83.7%; RR, 1.21; 95% CI, 1.00–1.46; $P = .05$; NNT, 6.9). Response to CIT was not statistically different from PLA (45.9% vs 37.9%; RR, 1.21; 95% CI, 0.82–1.81; $P = .35$; NNT, 12.4) at week 12 or at week 20 (69.3% vs 54.8%; RR, 1.26; 95% CI, 0.95–1.68; $P = .11$; NNT, 6.9). There was also no significant evidence for differences between CIT and PLA at 4 or 8 weeks. Results of sensitivity analyses did not differ from the main analyses for any of the comparisons, and results of adjusting only randomization stratification variables without race/ethnicity were nearly identical. There was no significant evidence of treatment effect heterogeneity across sites.

We hypothesized that participants with co-occurring MDD would show a greater difference between CIT and PLA than those without MDD. However, there was no significant evidence of an interaction between medication and MDD, with or without CGT (eAppendix 2 in Supplement 2). Replacing MDD by dichotomized severity of depressive symptoms (QIDS-SR_{16} score ≥16) did not change the results (eAppendix 2 in Supplement 2). However, depressive symptoms decreased significantly more with CGT when CIT was added (CGT with CIT vs CGT with PLA: QIDS-SR_{16} mean [standard error (SE)] difference, −2.06 [1.00]; 95% CI, −4.02 to −0.11; $P = .04$).Longitudinal analysis estimated a marginally significant QIDS-SR_{16} score mean [SE] difference of −1.24 (0.65; $P = .06$). Figure 2 displays observed mean trajectories of CG (ICG) and depressive (QIDS-SR_{16}) symptoms.

Outcome for Self-report Measures of Symptoms and Impairment

Results of inverse probability weighting–adjusted cross-sectional analyses of mean change in self-report ratings also closely mirrored the main outcome findings (Table 3). Citalopram and PLA showed no significant difference at week 12 for CG symptom severity (ICG-adjusted mean [SE] difference, 0.67 [2.04]; $P = .74$), grief-related impairment (WSAS-

adjusted mean [SE] difference, −0.84 [1.57]; $P = .59$), or grief-related avoidance (GRAQ-adjusted mean difference, −1.49 [1.56], $P = .34$); results were similar at week 20. Similarly, CIT with CGT and PLA with CGT were not statistically different on any of these measures at week 20. Citalopram with CGT was associated with significantly greater change than CIT (adjusted mean [SE] differences: ICG, −7.37 [2.08]; $P < .001$; WSAS, −4.13 [1.46]; $P = .005$; GRAQ, −5.19 [1.60]; $P = .001$), and PLA with CGT was associated with significantly greater change than PLA (adjusted mean [SE] differences: ICG, −8.01 [2.04]; $P < .001$; WSAS, −5.76 [1.63]; $P < .001$; GRAQ, −5.74 [1.43]; $P < .001$). Results from longitudinal analyses (mixed effects models) using all available assessments of symptom and impairment measures are consistent with inverse probability weighting analyses (eAppendix 3 in Supplement 2).

Treatment Effects on Suicidal Ideation

At the first treatment visit, rates of suicidal ideation on a clinician-rated suicide assessment were 30.6% for the CIT group, 32.2% for the PLA group, 32.2% for the CIT with CGT group, and 25.9% for the PLA with CGT group (Table 2). Those receiving medication without CGT still reported a wish to die at week 20 (CIT, 17.7%; PLA, 19.0%). Complicated grief treatment with CIT was associated with significantly lower suicidal ideation at week 20 compared with CIT (3.5% vs 17.7%; odds ratio, 0.17; 95% CI, 0.05–0.55; $P = .003$). Similarly, CGT with PLA at week 20 was significantly lower than PLA (6.7% vs 19.0%; odds ratio, 0.30; 95% CI, 0.11–0.85; $P = .02$).

Treatment Adherence—Seventy-four percent of those assigned to CGT completed all 16 sessions, and CIT did not significantly improve this completion rate (74.0% vs 73.7%; $P = .97$). Among participants not assigned to CGT, those receiving CIT were more likely to complete a full course of medication compared with those receiving PLA (62.4% vs 48.5%; $P = .05$). Medication adherence was greater with CGT with PLA than PLA (68.8% vs 48.5%; $P = .004$) but not significantly different for CGT with CIT compared with CIT (67.7% vs 62.4%; $P = .43$). Response rates for treatment completers were slightly higher for each treatment condition; however, results were not significantly different for any of our comparisons.

Adverse Effects of Treatment—We observed no serious adverse medication effects (eg, psychiatric or medical hospitalization, suicide attempts, or death [a participant in San Diego died by suicide during the study; review by the study team and institutional review board determined that this death was not related to the research]). Medication dose was adjusted to accommodate adverse effects as needed. Complicated grief treatment therapists monitored participant response to emotionally activating procedures, such as revisiting the death and confrontation with reminders of the deceased, and no serious untoward responses were documented.

Six-Month Follow-up—Data were obtained for 247 of 395 (62.5%) of all randomized and 247 of 289 (85.5%) of study completers. Rates of maintaining response at 6-month follow-up assessment were 96.4% for CGT with PLA, 93.1% for CGT with CIT, 96.4% for CIT without CGT, and 83.3% for PLA without CGT.

Discussion

Complicated grief is an underrecognized public health problem estimated to affect tens of millions of people worldwide.[1] Symptoms can be reliably assessed and are associated with a chronic course, high levels of suicidality,[26–28] and functional impairment comparable to many *DSM-5* disorders.[18] The severity and chronicity of distress and impairment underscore why intervening clinically with evidence-informed treatment is important. We conducted a randomized clinical trial to determine whether and how antidepressant medication should be used with and without psychotherapy to optimize treatment of CG.

Our results suggest the efficacy of CGT. To our knowledge, this is the third randomized clinical trial of CGT with positive findings and the first to compare it with PLA. Studies of similar psychotherapies have been published that further support the efficacy of this approach.[12,29] It is now clear in the first data from a multicenter trial that CGT or a similar psychotherapy is the treatment of choice for CG,[5,6,12,29–34] and it is important that clinicians know how to provide this treatment. Our results further indicate that adding antidepressant medication to CGT may not improve CG outcomes; however, medication is likely to improve results for co-occurring depressive symptoms.

Our conclusions regarding the use of antidepressant medication without CGT are less definitive. We did not find evidence for the efficacy of CIT monotherapy in this study at our planned 12-week end point or at any assessment before or after this (ie, 4, 8, 16, or 20 weeks). However, several issues reduce our confidence in considering this a definitive result. One consideration is that US Food and Drug Administration guidelines for CIT implemented more than a year after we initiated the study required us to decrease maximal daily dose from 60 mg to 40 mg. Although the 40-mg dose is consistent with prior studies documenting efficacy for depression,[35] it is possible that the response to CIT would have been greater if the higher dose were used. Another issue is that our recruitment rate was slightly lower than expected (90% of our target), and the assessment drop-out rate was over double what we expected. Although we included a statistical correction for assessment drop out, it is impossible to adjust fully for this problem. Citalopram outperformed PLA numerically on almost all analyses, with this difference most pronounced in those who had comorbid major depression at baseline. Citalopram was associated with significantly better adherence to treatment. Given these observations, we conclude that we have not disproved our initial belief that antidepressant medication can be helpful to people with CG (in the absence of appropriately targeted psychotherapy).

Other limitations include that our study sample was primarily white, female, and well-educated; results may not be generalizable to a more diverse sample. Pharmacotherapist use of CGT-informed clinical management and/or unique benefits of research participation may have inflated response rates; however, because study participants in all arms received these, efficacy results were not differentially impacted.

The robust PLA response rate in this study raises the possibility that pharmacotherapist behavior had a therapeutic effect. If so, physicians and other direct care professionals could improve the care of patients with CG if they learn to recognize CG, familiarize themselves

with assessment tools such as the ICG[8] and/or guided clinical interview for CG,[3] prepare to explain and monitor CG symptoms as different from depression,[36,37] and provide empathic support and gentle encouragement for re-engaging in daily activities. Behavioral medicine practitioners should learn to administer CGT.[3] Materials are available from http://www.complicatedgrief.columbia.edu/ to guide practitioners in achieving these goals.

Conclusions

In summary, CG is a serious, prevalent, and frequently chronic and debilitating condition that needs to be recognized and treated. Complicated grief treatment is the first-line treatment. Our results support the use of antidepressants in conjunction with CGT for relief of co-occurring depressive symptoms. When CGT is unavailable, CGT-informed supportive clinical management with or without antidepressants may be a helpful approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Does citalopram (CIT) enhance complicated grief treatment (CGT) outcome, and is CIT efficacious without CGT?

Findings

In this 4-site randomized clinical trial of 395 adults, there was a significantly greater rate of responders (ie, complicated grief much improved or very much improved) to CGT with placebo vs placebo. The addition of CIT did not improve the complicated grief response rate. However, depressive symptoms on the Quick Inventory of Depression Scale decreased significantly when CIT was added.

Meaning

Complicated grief treatment is the treatment of choice for complicated grief, and the addition of CIT optimizes treatment of co-occurring depressive symptoms.

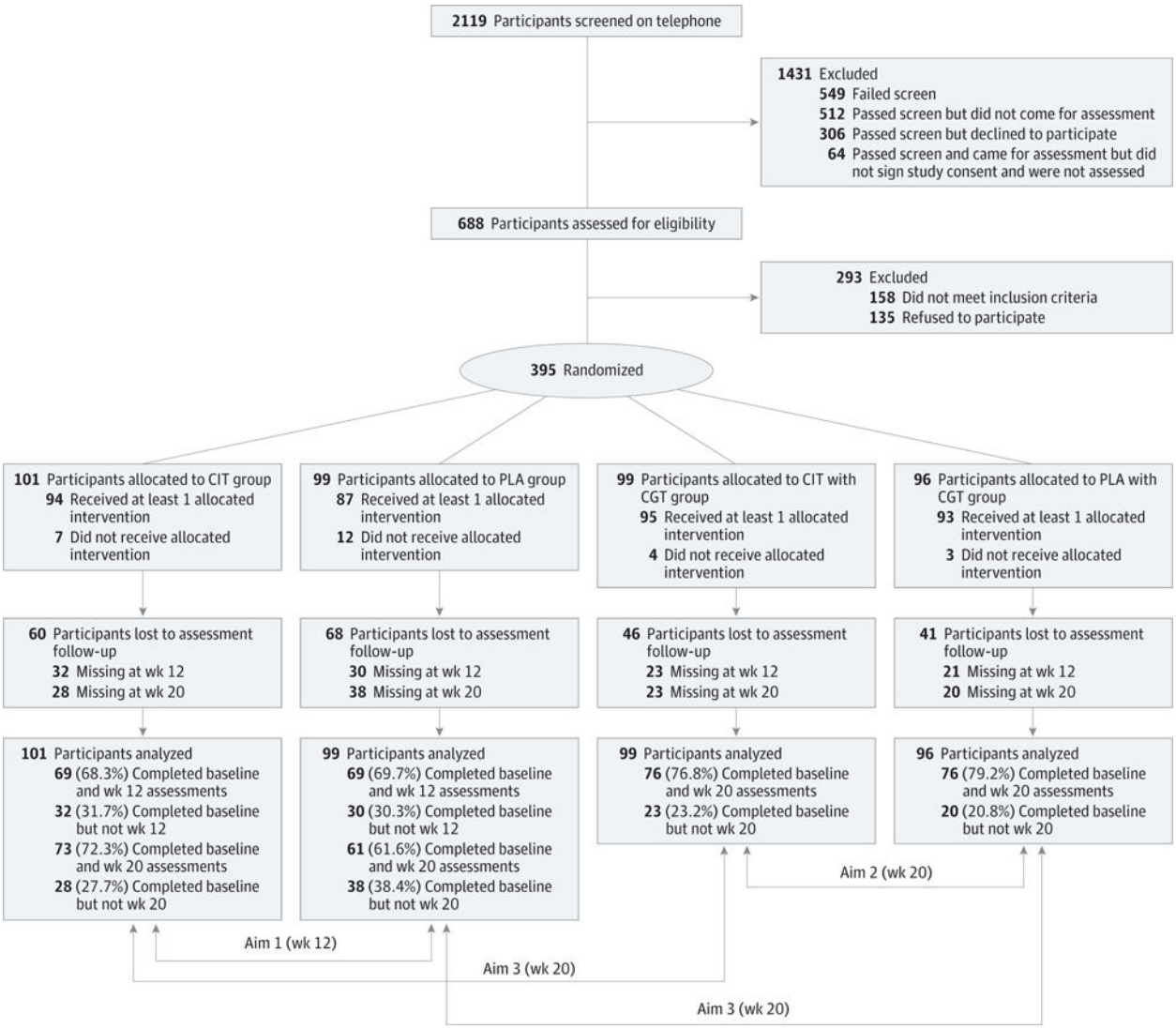

Figure 1. CONSORT Flowchart

CGT indicates complicated grief treatment; CIT, citalopram; PLA, placebo.

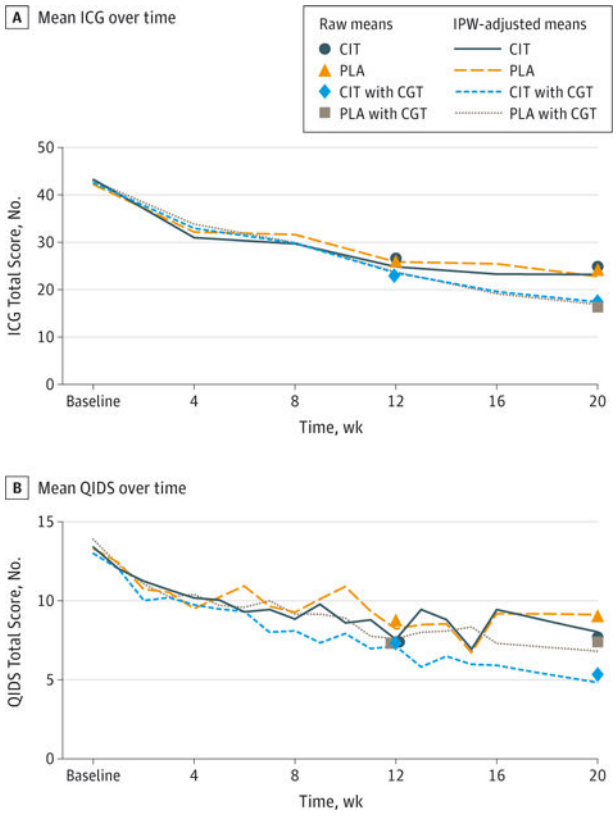

Figure 2. Inventory of Complicated Grief Scores

A, Scores on the Inventory of Complicated Grief (ICG) show improvement in participants randomized to complicated grief treatment (CGT) but no specific benefit of citalopram (CIT) relative to placebo (PLA). B, Depression self-ratings on the Quick Inventory of Depressive Symptoms (QIDS) show improvement when CIT is co-administered with CGT but little improvement in the absence of CGT. The ICG total score range is 0 to 76; the QIDS total score range is 0 to 27. IPW indicates inverse probability weighting.

Table 1

Complicated Grief–Clinical Global Impressions Scale–Severity and Improvement Items

Severity Rating	Severity Level Description	Improvement Rating	CG-CGI-Improvement Level Description
1. Normal	Feelings of grief are sometimes present but not intrusive. There is clear evidence of restoration of the capacity for joy and satisfaction in ongoing life. There is a sense of purpose in life and a feeling that happiness is possible.	1. Very much improved	There is clear evidence that distress and impairment from CG are markedly improved compared with baseline. The patient feels very differently about the role grief plays in her/his life compared with baseline. The CG-CGI-S score is usually no more than mild (3), but (rarely) may be moderate (4) if baseline severity was very high (7).
2. Borderline ill	Grief symptoms are present but rarely intrusive or distressing; there is little or no interference in activities and relationships and evidence of some capacity for pleasure and satisfaction.	2. Much improved	There is evidence that distress and impairment from CG are definitely improved compared with baseline, and this improvement is definitely clinically significant. The patient notices some difference in the role grief plays in her/his life. The CG-CGI-S score is usually no more than moderate (4). However, a patient can be much improved and grief symptoms may still be marked (5) if the baseline severity was very high (7).
3. Mildly ill	Symptoms of CG are present and sometimes intrusive and/or distressing but manageable, and there is minimal or no interference in functioning. There is engagement in activities and relationships with the potential for satisfaction and pleasure. Clinical significance is borderline or subthreshold.	3. Minimally improved	There is some evidence for improvement in distress and/or impairment from CG compared with baseline, but the clinical significance of the change is questionable or minimal.
4. Moderately ill	Symptoms of CG are present and intrusive on most days at a level that is painful but bearable. There is some interference with activities and relationships, but functioning is not substantially impaired. There may be some avoidance of reminders of the loss. A sense of purpose or meaning is usually present, but there may be confusion about this. Suicidal thoughts may be present, but there is usually a desire to live. Distraction is possible temporarily, but symptoms are persistent and clinically significant.	4. No change	Distress and impairment from CG have not changed in any meaningful way since the baseline assessment.
5. Markedly ill	Symptoms of CG are frequent and intrusive at a level that causes substantial pain and definite interference with functioning. There is usually some avoidance of reminders of the loss, loss of a sense of purpose or meaning in life, and/or a feeling that joy and satisfaction are no longer possible; suicidal thoughts are usually present and may be prominent. There may be a feeling of just waiting to die. There is little relief from CG symptoms; distraction is difficult and, when possible, short-lived.	5. Minimally worse	There is evidence that distress or impairment from CG is somewhat worse since the baseline assessment, but the clinical significance of this change is questionable or minimal.
6. Severely ill	Symptoms of CG are nearly constant and preoccupying on most days at a level that is severe and impairing; extensive avoidance is often present. There is often a belief that joy and satisfaction are no longer possible; there may be active suicidal ideation or indirect suicidal behavior. Distraction is rarely possible and only partially effective, and there may be periods of inability to function.	6. Much worse	There is evidence that distress and impairment from CG are definitely worse since the baseline assessment, and this change is clinically significant. Alternative care should be considered.

Severity Rating	Severity Level Description	Improvement Rating	CG-CGI-Improvement Level Description
7. Among the most extremely ill patients	Symptoms of CG are present continuously or nearly continuously at a very severe level. The person is virtually unable to function in activities or relationships. There may be strongly held self-blaming or accusatory beliefs about the death that border on delusional. There is a conviction that joy and satisfaction are no longer possible. Avoidance is usually present and extensive. Active suicidal thoughts or indirect suicidal behavior are usually present.	7. Very much worse	There is evidence that distress and impairment from CG are markedly worse since the baseline assessment. There may be emergent clinically significant suicidal thinking or behavior or risk of other serious consequences of worsening grief. Alternative care is definitely needed.

Abbreviations: CG, complicated grief; CGI, Clinical Global Impression scale; CG-CGI-S, Complicated Grief–Clinical Global Impressions Scale–Severity.

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Table 2

Comparison of Treatment Groups[a]

Characteristic	No. (%)					Test Statistic	*P* Value
	Total (n = 395)	CIT (n = 101)	PLA (n = 99)	CIT With CGT (n = 99)	PLA With CGT (n = 96)		
Male	87 (22.0)	19 (18.8)	30 (30.3)	21 (21.2)	17 (17.7)	5.64	.13
Race							
White	325 (82.3)	85 (84.2)	80 (80.8)	81 (81.8)	79 (82.3)	2.50	.87
Black	39 (9.9)	10 (9.9)	8 (8.1)	11 (11.1)	10 (10.4)		
Others	31 (7.8)	6 (5.9)	11 (11.1)	7 (7.1)	7 (7.3)		
Hispanic or Latino	45 (11.4)	10 (9.9)	7 (7.1)	8 (8.1)	20 (20.8)	11.61	.01
Education							
≤12 y	45 (11.4)	9 (8.9)	10 (10.1)	14 (14.1)	12 (12.5)	1.95	.92
Partial college	139 (35.2)	36 (35.6)	37 (37.4)	32 (32.3)	34 (35.4)		
≥ 4 y college	211 (53.4)	56 (55.4)	52 (52.5)	53 (53.5)	50 (52.1)		
Marital status							
Never	97 (24.6)	22 (21.8)	21 (21.2)	29 (29.3)	25 (26.0)	5.56	.78
Married	92 (23.3)	27 (26.7)	27 (27.3)	20 (20.2)	18 (18.8)		
Separated/divorced	68 (17.2)	18 (17.8)	15 (15.2)	15 (15.2)	20 (20.8)		
Widowed (not remarried)	138 (34.9)	34 (33.7)	36 (36.4)	35 (35.4)	33 (34.4)		
Person who died							
Spouse/partner	144 (36.5)	37 (36.6)	38 (38.4)	36 (36.4)	33 (34.4)	4.86	.85
Parent	113 (28.6)	30 (29.7)	28 (28.3)	32 (32.3)	23 (24.0)		
Child	80 (20.3)	21 (20.8)	21 (21.2)	15 (15.2)	23 (24.0)		
Other	58 (14.7)	13 (12.9)	12 (12.1)	16 (16.2)	17 (17.7)		
Cause of death							
Illness >1 mo	80 (20.3)	23 (22.8)	18 (18.2)	20 (20.2)	19 (19.8)	13.19	.59
Illness <1 mo	175 (44.3)	38 (37.6)	52 (52.5)	43 (43.4)	42 (43.8)		
Accident	58 (14.7)	19 (18.8)	7 (7.1)	14 (14.1)	18 (18.8)		
Murder	16 (4.1)	5 (5.0)	4 (4.0)	4 (4.0)	3 (3.1)		

Characteristic	No. (%)					Test Statistic	*P* Value
	Total (n = 395)	CIT (n = 101)	PLA (n = 99)	CIT With CGT (n = 99)	PLA With CGT (n = 96)		
Suicide	58 (14.7)	14 (13.9)	17 (17.2)	14 (14.1)	13 (13.5)		
Other	8 (2.0)	2 (2.0)	1 (1.0)	4 (4.0)	1 (1.0)		
Violent death	132 (33.4)	38 (37.6)	28 (28.3)	32 (32.3)	34 (35.4)	2.20	.53
Current MDD	262 (66.3)	68 (67.3)	66 (66.7)	64 (64.6)	64 (66.7)	0.18	.98
Current PTSD	154 (39.0)	41 (40.6)	36 (36.4)	37 (37.4)	40 (41.7)	0.79	.85
Clinical Global Impression Scale-Severity							
Moderately ill[b]	130 (32.9)	37 (36.6)	30 (30.3)	36 (36.4)	27 (28.1)		
Markedly ill	199 (50.4)	47 (46.5)	49 (49.5)	46 (46.5)	57 (59.4)	5.57	.47
Severely/Extremely ill	66 (16.7)	17 (16.8)	20 (20.2)	17 (17.2)	12 (12.5)		
Columbia Suicide scale							
Before death, wish to be dead	131 (33.2)	32 (31.7)	33 (33.3)	34 (34.3)	32 (33.3)	0.16	.98
Before death, nonspecific active suicidal thoughts	73 (18.5)	17 (16.8)	19 (19.2)	16 (16.2)	21 (21.9)	1.30	.73
Since death, wish to be dead	221 (55.9)	60 (59.4)	51 (51.5)	57 (57.6)	53 (55.2)	1.41	.70
Since death, nonspecific active suicidal thoughts	103 (26.1)	25 (24.8)	31 (31.3)	25 (25.3)	22 (22.9)	2.03	.57
Clinician-rated suicide assessment at wk 1 (n = 351)	105 (30.3)	26 (30.6)	28 (32.2)	29 (32.2)	22 (25.9)	1.09	.78
Inventory of Complicated Grief, mean (SD)	42.8 (8.9)	43.2 (8.5)	42.2 (9.4)	42.6 (9.4)	43.0 (8.3)	0.24	.87
Work and Social Adjustment scale, mean (SD)	22.3 (9.8)	22.0 (9.6)	23.2 (10.1)	21.8 (9.6)	22.2 (9.9)	0.43	.73
Grief-Related Avoidance Questionnaire, mean (SD)	22.7 (13.0)	22.2 (13.2)	22.6 (12.0)	22.6 (12.4)	23.5 (14.5)	0.16	.92
Structured Clinical Interview for CG score, mean (SD)[c]	66.3 (9.2)	66.2 (9.7)	66.5 (10.0)	66.6 (8.8)	66.1 (8.3)	0.06	.98
Age, mean (SD)	53.0 (14.5)	52.4 (13.1)	53.9 (13.8)	52.1 (15.3)	53.5 (16.0)	0.35	0.79
Years since loss, mean (SD)	4.7 (7.2)	4.6 (5.8)	5.3 (8.7)	4.7 (7.5)	4.3 (6.7)	0.36	0.78

Abbreviations: CG, complicated grief; CGT, complicated grief treatment; CIT, citalopram; MDD, major depressive disorder; NA, not applicable; PLA, placebo; PTSD, posttraumatic stress disorder.

[a] χ^2 tests were used to compare group differences at baseline for categorical outcomes; analysis of variance tests were used for continuous outcomes.

[b] Includes 2 individuals who were rated as *mildly ill* but had other assessment ratings more consistent with *moderately ill.*

[c] Data available for 306 participants.

Table 3

IPW-Adjusted Mean Differences in the Secondary Outcomes for Each Hypothesis[a]

	Aim 1: CIT vs PLA (wk 12)		Aim 2: CIT With CGT vs PLA With CGT (wk 20)		Aim 3: CIT With CGT vs CIT (wk 20)		Aim 3: PLA With CGT vs PLA (wk 20)	
Test	**IPW-Adjusted Difference, Mean (SE)**	***P* Value**	**IPW-Adjusted Difference, Mean (SE)**	***P* Value**	**IPW-Adjusted Difference, Mean (SE)**	***P* Value**	**IPW-Adjusted Difference, Mean (SE)**	***P* Value**
ICG	0.67 (2.04)	.74	1.26 (1.98)	.53	−7.37 (2.08)	<.001[b]	−8.01 (2.04)	<.001[b]
WSAS	−0.84 (1.57)	.59	1.20 (1.44)	.40	−4.13 (1.46)	.005[b]	−5.76 (1.63)	<.001[b]
QIDS	−1.37 (0.89)	.12	−2.06 (1.00)	.04[b]	−2.35 (1.13)	.04[b]	−1.61 (1.15)	.16
GRAQ	−1.49 (1.56)	.34	1.14 (1.38)	.41	−5.19 (1.60)	.001[b]	−5.74 (1.43)	<.001[b]

Abbreviations: CIT, citalopram; CGT, complicated grief treatment; GRAQ, Grief-Related Avoidance Questionnaire; ICG, Inventory of Complicated Grief; IPW, inverse probability weighting; PLA, pill placebo; QIDS, Quick Inventory of Depressive Symptoms; SE, standard error; WSAS, Work and Social Adjustment Scale.

[a]Results obtained by weighted linear regressions of the secondary outcomes measured at primary time points (week 12 or week 20), controlling for site, baseline major depressive disorder, and race/ethnicity and with inverse probability weighting to account for missing assessment data.

[b]Significant at a significance level of $P < .05$.