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The impact of concurrent naturalistic pharmacotherapy on psychotherapy of complicated grief

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Abstract

Complicated grief (CG) is a debilitating syndrome that can be reliably identified, but there is a paucity of research examining treatment of CG. A targeted psychotherapy for complicated grief (CGT) was recently proven efficacious (Shear et al., 2005). We provide a detailed examination of the association of naturalistic pharmacotherapy use with treatment response and study completion in the psychotherapy study. Patients on an antidepressant medication were more likely to complete a full course of CGT (91% vs. 58% completed: p=0.007), while antidepressant use had no effect on completion rates for the comparator, interpersonal psychotherapy (70% vs. 77%). Our naturalistic data underscore the need for prospective, randomized controlled studies of CG pharmacotherapy and psychotherapy alone and in combination.

Keywords

treatment; antidepressant; benzodiazepine; complicated grief; traumatic grief; prolonged grief

1. Introduction

Complicated grief (CG) is a debilitating syndrome that can be reliably identified. CG is diagnosed when intense grief persists more than 6 months after the loss of a loved one. Symptoms include separation distress (recurrent pangs of painful emotions, with intense yearning and longing for the deceased, and preoccupation with thoughts of the loved one) and traumatic distress (sense of disbelief regarding the death, anger and bitterness, distressing, intrusive thoughts related to the death, and pronounced avoidance of reminders of the painful loss) (Shear et al., 2005).

While CG causes significant distress and impairment (Shear et al., 2005) (Silverman et al., 2000) and is associated with excess medical morbidity and suicidality (Prigerson et al.,

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1997; Prigerson et al., 1999; Szanto et al., 2006), little is known about its treatment. Pharmacotherapy studies primarily targeting bereavement-related depression found minimal to modest effects of medication on grief (Zygmont et al., 1998; Reynolds et al., 1999; Zisook et al., 2001). Zisook and colleagues treated 22 individuals who met criteria for a major depressive episode (allowing bereavement) six to eight weeks after a loss with open-label bupropion, and found significant reduction in depression, with modest though statistically significant concurrent decreases in grief symptoms in this acute period (Zisook et al., 2001). Zygmont and colleagues openly treated 15 individuals with complicated grief 6 to 17 months after a loss with paroxetine (median dose 30mg/day) for 4 months concurrent with a grief focused psychotherapy and found a similar reduction in grief symptoms as a historically treated group of 22 individuals treated with nortriptyline for bereavement related depression; however, the study design did not allow separation of paroxetine effects from psychotherapy effects (Zygmont et al., 1998). In the only relevant RCT to date, Reynolds and colleagues examined the impact of nortriptyline, interpersonal psychotherapy or the combination on bereavement related major depressive episodes in 80 patients aged 50 and older, and found that while there were antidepressant effects in this population with nortriptyline, neither IPT or nortriptyline led to a significant reduction in grief symptoms (Reynolds et al., 1999), consistent with their open pilot study of nortriptyline in bereavement related depression which failed to reduce grief intensity (Pasternak et al., 1991).

We thus developed Complicated Grief Therapy (CGT), which was demonstrated efficacious compared to interpersonal psychotherapy (IPT) in the first randomized controlled trial (RCT) of a treatment for CG (Shear et al., 2005). The active control condition, interpersonal therapy with a grief focus, followed a standard published manual (Wiessman et al., 2000). Briefly, interpersonal therapy has an introductory phase when symptoms and an interpersonal inventory are reviewed, a middle phase that addresses grief symptoms, interpersonal problems (as well as specifically addressing the positive and negative aspects of the patient's relationship with the deceased person), and encouraging participation in satisfying activities and relationships, and a termination phase. Complicated Grief Therapy (CGT) similarly followed a manual and consists of an introductory, middle and termination phase. The introductory phase has a greater focus on psychoeducation about the difference between normal and complicated grief, information about the "dual process" model of adapting to loss including adjustment to loss of the loved one alongside increased focus on personal goals and restoration of life satisfaction. In addition to working directly with personal goals throughout the treatment, the middle phase of CGT included loss-focused elements adapted from exposure therapy techniques, including telling and listening to tapes of the story of the death ("revisiting"), hierarchical exposure to avoided reminders of the loss, direct work with positive and negative memories of the deceased, and an imaginal conversation with the deceased person. CGT and IPT were each 16 sessions in length. In the overall RCT, CGT resulted in a significantly greater proportion of treatment responders than IPT in both the intent to treat (51% CGT vs. 28 IPT, $p=0.02$) and the completers only analyses (66% CGT vs. 32% IPT, $p=0.006$).

Stable medication use was permitted during the psychotherapy study; we previously reported that 45% (43/95) of RCT participants were taking an antidepressant, and initial analyses found non-significant differences in outcome for those on an antidepressant medication (Shear et al., 2005). Given the dearth of information about treatment of CG, we now present detailed secondary analyses of naturalistic pharmacotherapy use and its association with response and completion of CGT and IPT in the trial. To our knowledge, this is the first study to examine the impact of concurrent medication use on two different types of psychotherapy.

2. Methods

Detailed methodology of the parent RCT are available elsewhere (Shear et al., 2005). Briefly, eligible individuals had ≥ 6 months of persistent grief with CG their primary clinical problem (as confirmed by an independent evaluator), and scored ≥ 30 on the Inventory of Complicated Grief (ICG), a 19-item scale with a total score range of 0 to 76 (Prigerson et al., 1995). Comorbid AXIS I psychiatric disorders were diagnosed utilizing the Structured Clinical Interview for DSM-IV (First, 1994). Response was defined as a score of 1 or 2 ("very much improved" or "much improved") on the Clinical Global Impression of Improvement Scale (CGI-I: scale range 1 to 7, with 4= "no change" and 7="very much worse" (Guy, 1976)) focused specifically on CG symptoms. Medication use of ≥ 3 months duration at stable dose for ≥ 6 weeks was permitted if medication management was transferred to our study pharmacotherapist. Medication could not be increased; although patients were encouraged to maintain stable doses, dose reduction was permitted.

We examined medication use amongst the 95 randomized participants and its relationship with treatment response and study completion overall and separately for CGT and IPT. Medication history was obtained using study forms and review of written records by our pharmacotherapist (AF). We classified psychiatric medications as: antidepressants, benzodiazepines, antipsychotics, anticonvulsants, or other central nervous system agents (e.g., low dose trazodone).

2.1 Statistical Methods

Logistic regression analyses examined prediction of treatment response (CGI-I responder status) by medication use, first univariately and then with covariates for age, gender, race and current psychiatric comorbidity entered together to control for potential confounding. Univariate and adjusted models were run for each of the following medication groups: any psychiatric medication, benzodiazepines, and antidepressants. Study completion data were similarly analyzed with logistic regressions, univariately and adjusted for the presence of comorbidity. Binary baseline data were tested with Fisher's Exact Test (FET). Baseline continuous measures were examined with t-tests, after assessing normality. Statistical significance was set at $P \leq 0.05$, with no adjustment for multiple testing.

3. Results

3.1 Pharmacotherapy Use and Baseline Characteristics in the Randomized Trial (n=95)

Demographic data have been previously published (Shear et al., 2005). Briefly, the sample was 87% female, 76% Caucasian, with a mean (SD) age of 48.4 ± 12.7 years, and a mean baseline ICG score of 45.4 ± 8.6. With regards to comorbidity, 70.5% of the sample had a current comorbid mood or anxiety disorder. Current major depressive disorder (MDD) was diagnosed in 46.3% of the sample, while 59.0% had at least one current anxiety disorder (48.4% current posttraumatic stress disorder, 10.5% current panic disorder, 6.3% current obsessive compulsive disorder, 3.2% current social anxiety disorder). Psychiatric medication use was common, with 52.6% (n=50) on at least one psychiatric medication, 20% (n=19) on a benzodiazepine, 6.3% (n=6) on an anticonvulsant, 4.2% (n=4) on an antipsychotic, and 45.3% (n=43) on an antidepressant. Of note, of those on an antidepressant, 32% were on more than one antidepressant, 51% were on at least one other agent, and 35% were taking a concurrent benzodiazepine.

There was no significant difference in baseline CG severity for those on an antidepressant (mean ICG= 45.9±9.5) vs. not (ICG= 44.3± 8.6). There was, however, significantly greater antidepressant use in those with at least one comorbid mood or anxiety disorder (53.7% (36/67)) compared to those without (25% (7/28): FET P =0.013). More specifically, 61.4%

(27/44) of those with comorbid current MDD were on an antidepressant, compared to only 31.4% (16/51) without (FET *P* =0.004), while 57.6% (38/66) with lifetime MDD were on an antidepressant currently compared to 17.2% (5/29) of those without.

3.2 Pharmacotherapy and Treatment Outcomes in the Psychotherapy Trial

Table 1 presents psychotherapy response rates among those with and without concurrent pharmacotherapy. For the full study sample (n=95), current antidepressant use was significantly associated with a more than doubling of the odds of treatment response in both univariate (OR=2.4) and adjusted (OR=2.7) analyses (see Table 1). For the CGT group alone, those on an antidepressant had a 61% response rate compared to 42% of those not; however, no psychiatric medication was associated with a statistically significant difference in response rate to CGT in either univariate or demographic and comorbidity adjusted analyses (see Table 1). By contrast, our data suggest current concomitant medication use (notably benzodiazepines), was of significant benefit for the individuals with CG receiving IPT (see Table 1).

3.2 The Effect of Pharmacotherapy on Drop Out in the Psychotherapy Trial

Data regarding the association of pharmacotherapy with study completion are presented both univariately and adjusted for psychiatric comorbidity in Table 2. Overall, there was no difference in study completion rates for CGT (73.5%) compared with IPT (73.9%). However, use of antidepressants was associated with a significantly higher odds of CGT completion compared with those not on an antidepressant in both univariate (OR=7.7) and comorbidity adjusted analyses (OR=6.3: see Table 2). The presence of antidepressants did not, however, impact IPT completion. Benzodiazepine use was not associated with study completion (see Table 2).

4. Discussion

Several findings from our data are of interest. First, more than half of this treatment-seeking CG sample was currently using psychiatric medication, which was not associated with different levels of grief. Not surprisingly, antidepressant use was most common, and greater in those with comorbid depression or anxiety disorders. Since we clearly did not recruit individuals with CG who remitted with medication alone, it is impossible to determine how effective medication alone might be for this population and randomized controlled studies are needed. Consistent with several prior studies that have shown modest response of grief symptoms to antidepressants, however, the presence of a highly symptomatic, treatment seeking group of patients with CG despite the use of antidepressants suggests at least some patients do not remit on antidepressants (Pasternak et al., 1991; Reynolds et al., 1999; Zisook et al., 2001).

The presence of naturalistic psychotropic medication use was associated with some interesting suggestive differences in psychotherapy response and discontinuation rates. Surprisingly, the association of response and discontinuation during the psychotherapy trial with the presence of current medication use appeared to differ based on the type of psychotherapy. While our results are clearly preliminary since medication use was not studied experimentally and power was limited, they suggest that different types of medication may be useful for different types of psychotherapy in different ways. We are unaware of prior literature raising this possibility for mood or anxiety related disorders.

CGT is a focused, short-term psychotherapy that includes emotionally demanding elements such as retelling and listening to the story of the death, and other exposure tasks and assignments. Potential improvements in associated mood, motivation, sleep, and or

emotional tolerance associated with pharmacotherapy each offer possible explanations for our suggestive findings that those on antidepressants may be better able to tolerate and complete CGT, while these issues may be less relevant for IPT completion, although we did not able to directly examine these hypotheses in this dataset. Our combined treatment findings for IPT and pharmacotherapy are similar to the Reynolds and colleagues RCT finding that IPT combined with nortriptyline was effective for bereavement related major depression while IPT alone was not (although neither had strong effects specifically for grief in (Reynolds et al., 1999). Reasons for the relatively greater response in the IPT plus pharmacotherapy group in our CG trial compared to IPT alone are not clear and require replication; however, given the generally low response of CG to IPT, the control condition for the trial, it is possible that the effects are primarily due to medication effects over time. This hypothesis could not be examined in this study, which lacked a medication only condition.

Our results must be considered provisional because medication was provided naturalistically (i.e., without random assignment), and there was no pill placebo or other control comparison group. Unlike the gold standard randomized, placebo controlled clinical trial (RCT), the presence of uncontrolled and possibly unmeasured biases influencing treatment selection may influence outcomes in naturalistic data. . Our data are derived from a treatment seeking population, who are likely to have a greater severity of grief symptoms, higher rates of comorbidity, and a greater likelihood of receiving pharmacotherapy than a community based sample. Although participants taking antidepressant medication had a higher frequency of mood and anxiety disorders, we were unable to determine for what disorder medication was initiated, and whether or not medicated individuals had improved since initiating pharmacotherapy. The study was also not designed or powered to answer questions about combined treatment.

While conclusions from our data should be considered preliminary, and require confirmation in a well-powered RCT, given the paucity of data in this field they do offer some initial insights and directions for future research. For example, despite these limitations, our data suggest there is significant use of medication in this population. While participants with comorbid MDD were more likely to receive antidepressants, patients without comorbidity were also receiving medication. This is notable given the lack of any agent with RCT data supporting its safety and efficacy for CG. Our data also suggest that medication may have different effects on outcome with different types of therapy for CG. Our strongest finding was that concurrent antidepressant medication greatly increased CGT study completion, while having no effect at all on IPT completion. Taken together, our results suggest that prospective RCTs examining the role of pharmacotherapy for the treatment of CG with and without concomitant psychotherapy are needed.

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Table 1

Association of Current Naturalistic Pharmacotherapy with Treatment Response to Complicated Grief Therapy (CGT) and to Interpersonal Therapy (IPT) in a Psychotherapy Trial of Complicated Grief

	CGI-I RESPONSE RATE Overall (n=95)				CGI-I RESPONSE RATE CGT (n=49)				CGI-I RESPONSE RATE IPT (n=46)			
	Meds present	**Meds absent**	**Univariate OR 95% CI**	**Adjusted OR 95% CI**	**Meds present**	**Meds absent**	**Univariate OR 95% CI**	**Adjusted OR 95% CI**	**Meds present**	**Meds absent**	**Univariate OR 95% CI**	**Adjusted OR 95% CI**
At least one medication	46.8% 22/47	33.3% 16/48	1.8 0.77–4.0	2.0 0.82–4.8	53.6% 15/28	47.6% 10/21	1.1 0.35–3.3	1.0 0.31–3.4	38.1% 8/21	20.0% 5/25	2.8 0.75–10.5	3.9 *t* 0.82–18.7
At least one benzodiazepine	50.0% 10/20	37.3% 28/75	1.7 0.62–4.5	1.7 0.59–4.8	44.4% 4/9	52.5% 21/40	0.7 0.17–3.1	0.6 0.14–3.0	50.0% 5/10	22.2% 8/36	4.8* 1.13–20.4	5.3* 1.03–27.4
At least one antidepressant	51.2% 22/43	30.8% 16/52	2.4* 1.02–5.5	2.7* 1.1–6.8	60.9% 14.23	42.3% 11/26	2.1 0.68–6.7	2.1 0.59–7.3	40.0% 8/20	19.2% 5/26	2.8 0.75–10.5	4.8*t* 0.90–25.6

Odds Ratio (OR) and 95% confidence interval from logistic regression model of Clinical Global Impression of Improvement (CGI-I) responder status: Univariate OR presented first, Adjusted OR includes adjustment for age, gender, race and psychiatric comorbidity.

* denotes *P* value <0.05 for OR of medication covariate in regression model.

t = statistical trend (*P* <0.10).

Table 2

Association of Current Naturalistic Pharmacotherapy with Completion Rates for Complicated Grief Therapy (CGT) and Interpersonal Therapy (IPT) in a Psychotherapy Trial of Complicated Grief

	Overall Completion Rates (n=95)				CGT Completion Rates (n=49)				IPT Completion Rates (n=46)			
	Meds present	Meds absent	Univariate OR 95% CI	Adjusted OR 95% CI	Meds present	Meds absent	Univariate OR 95% CI	Adjusted OR 95% CI	Meds present	Meds absent	Univariate OR 95% CI	Adjusted OR 95% CI
At least one medication	75.5% 37/49	71.7% 33/46	1.2 0.49–3.0	1.2 0.46–3.0	78.6% 22/28	66.7% 14/21	1.8 0.51–6.6	1.5 0.38–5.6	71.4% 15/21	76.0% 19/25	0.8 0.21–3.0	1.0 0.25–4.0
At least one benzodiazepine	73.7% 14/19	73.7% 56/76	1.0 0.32–3.1	1.0 0.32–3.1	66.7% 6/9	75.0% 30/40	0.7 0.14–3.2	0.7 0.14–3.7	80.0% 8/10	72.2% 26/36	1.8 0.33–9.8	1.6 0.28–9.25
At least one antidepressant	81.4% 35/43	67.3% 35/52	2.1 0.81–5.6	2.1 0.80–5.8	91.3% 21/23	57.7% 15/26	7.7* 1.48–39.9	6.3* 1.18–34.2	70.0% 14/20	76.9% 20/26	0.7 0.19–2.6	0.9 0.21–3.4

Odds Ratio (OR) and 95% confidence interval from logistic regression model of completer status: Univariate OR presented first, Adjusted OR includes adjustment for psychiatric comorbidity.

*denotes *P* value <0.05 for OR of medication covariate in regression model.