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_____	_____
Jamie C. Kennedy	Date

Follow-up of Monotherapy Remitters in the PReDICT Study:
Maintenance Treatment Outcomes and Clinical Predictors of Relapse and Recurrence

By

Jamie C. Kennedy
Master of Arts
Psychology

_____
W. Edward Craighead, Ph.D.
Advisor

_____
Linda W. Craighead, Ph.D.
Committee Member

_____
Hillary R. Rodman, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

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By

Jamie C. Kennedy
B.A., University of Colorado at Boulder, 2004
M.B.A., Stanford Graduate School of Business, 2010

Advisor: W. Edward Craighead, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
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Abstract

Follow-up of Monotherapy Remitters in the PReDICT Study:
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By Jamie C. Kennedy

This study followed remitted patients from a randomized controlled trial of adults with Major Depression. The aims were to describe rates of relapse and recurrence and to evaluate three clinical predictor domains. Ninety-four treatment naïve patients (50% female; M_{age} = 38.1; 48.9% Caucasian) with Major Depression who had remitted to 12-week monotherapy (escitalopram, duloxetine, or cognitive-behavior therapy (CBT)) participated in a 21-month maintenance phase (i.e., continued medication or up to 3 CBT booster sessions per year). Relapse and recurrence were operationalized as the single construct of relapse/recurrence and were assessed quarterly. The clinical predictors were: two measures of residual depressive symptoms, one measure of prior depressive episodes, and two measures of baseline anxiety. Standard survival analysis methods were used for the analyses. An estimated 15.5% of patients suffered a relapse/recurrence, and the survival distributions did not statistically differ across treatment conditions. Residual depressive symptoms on the Hamilton Rating Scale for Depression were associated with increased risk in relapse/recurrence (Hazard Ratio = 1.31, 95% CI [1.02., 1.67], Wald X^2 = 4.41, p = .036), as was a comorbid anxiety disorder diagnosis at study baseline (Hazard Ratio = .31, 95% CI [.10, .94], Wald X^2 = 4.28, p = .039). Both variables were marginally significant in a multivariate model, and none of the other clinical measures were statistically significant in any of the analyses. The current study supports the benefits of maintenance treatment for most treatment naïve patients who remit to initial monotherapy. However, patients with residual depressive symptoms after initial treatment or a comorbid anxiety disorder diagnosis at the beginning of treatment are at risk for poorer long-term outcomes despite achieving remission.

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There is substantial evidence that antidepressant medications and evidenced-based psychotherapies can effectively help depressed individuals (Cuijpers, van Straten, Warmerdam, & Andersson, 2008; Spielmans, Berman, & Usitalo, 2011). Many such individuals, however, face a significant risk of depressive relapse or recurrence following successful treatment of the acute depressive episode. Relapse is the return of symptoms associated with an original "index" depressive episode, and recurrence refers to the development of a new episode following recovery, a prolonged and largely asymptomatic period (Frank et al., 1991; Rush et al., 2006). High rates of depressive relapse and recurrence have been reported in clinical cohort studies (e.g., Judd et al., 2016), population studies (e.g., Moffitt et al., 2010), community studies (e.g., Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013), and in the placebo condition of treatment studies (Geddes et al., 2003).

Due to the long-term course of major depressive disorder (MDD), clinical guidelines recommend that treatment continue well beyond the point of initial treatment response. For example, the American Psychiatric Association (APA) recommends that patients who remit to evidence based psychotherapy and/or antidepressant medications continue treatment for an additional 4 - 9 months after remission (APA, 2010). The guidelines further recommend that clinicians consider maintaining treatment for longer if the patient is deemed to be at-risk for recurrence (e.g., at end of treatment the patient still has subthreshold symptoms, a history of multiple depressive episodes, or psychiatric comorbidity). Similarly, the British National Institute for Health and Care Excellence (NICE) recommends that patients continue treatment for 6 - 12 months after initial treatment response and also maintain treatment beyond this time period if they are at-risk for recurrence (NICE, 2010).

Antidepressant medications (ADMs) are the most widely used treatment for MDD (Olfson & Marcus, 2009), and patients who respond to ADMs and continue to use them appear to have a lower risk of relapse and recurrence than patients who discontinue medications after a treatment response. One meta-analysis (Geddes et al., 2003) of 31 randomized trials of patients who had responded to ADMs found that patients randomized to the continued use of ADMs had a lower risk of relapse than patients randomized to ADM discontinuation via pill-placebo (OR = .30, 95% CI [.22, .38], $p < .001$). The results were similar for all included classes of antidepressants with an average relapse rate of 19% for ADMs and 41% for placebo. The treatment effect appeared to last up to 36 months, although most of the included trials were limited to 12 months of follow-up. A more recent meta-analysis (Glue, Donovan, Kolluri, & Emir, 2010) reached a similar conclusion, as did an extensive review of maintenance trials published by the U.S. Food and Drug Administration (Borges et al., 2014).

Cognitive-Behavior Therapy (CBT), an evidenced-based psychotherapy and alternative first-line treatment approach to ADMs, also appears to reduce the risk of relapse and recurrence. An influential meta-analysis (Cuijpers et al., 2013) found that patients initially treated with CBT were less likely to relapse than patients who were successfully treated with ADMs and then withdrawn from treatment (OR = 2.61, 95% CI [1.58., 4.31], $p < .001$). This study also reported there was no difference in relapse rates between patients who responded to initial CBT and patients who responded to initial ADMs and continued to use them (OR = 1.62, 95% CI [.97, 2.72]). Two prior studies most relevant to the current study and included in the Cuijpers and colleagues' meta-analysis are described below.

Hollon and colleagues (2005) compared long-term outcomes of 104 treatment responders who continued their initial treatment through one year of follow-up. Patients who responded to

ADM (paroxetine, plus possible augmentation with either lithium or desipramine) were randomized either to continued ADM or placebo withdrawal, and CBT patients were offered "booster" sessions (0-3) during the follow-up period. Relative to patients withdrawn from medications to placebo, patients treated with initial CBT were less likely to relapse (adjusted relapse rates: 30.8% vs. 76.2%, $p = .004$), and patients continued on ADMs were less likely to relapse at the level of a nonsignificant trend (adjusted relapse rates: 47.2% vs. 76.2%, $p = .08$). Rates of relapse did not differ between CBT patients and patients continued on ADMs (adjusted relapse rates: 30.8% vs. 47.2%, $p = .20$). At the end of the first year of follow-up, continuation ADM patients were withdrawn from medication, and all surviving patients continued in the study for one year of naturalistic follow-up. During this one-year follow-up period, prior CBT was more effective in preventing recurrence than prior ADM treatment (adjusted recurrence rates: 17.3% vs. 53.6%, $p = .009$).

Dobson and colleagues (2008) compared the long-term outcomes of 106 patients who had responded to CBT, Behavioral Activation (BA), or ADM (paroxetine). Following initial treatment, patients who responded to ADM were randomized to either continued ADM or were withdrawn from treatment and placed on placebo. Compared to patients withdrawn from ADM, patients treated with prior CBT were less likely to relapse (adjusted relapse rates: 39% vs. 59%, $p = .04$), and patients treated with prior BA were less likely to relapse at the level of a nonsignificant trend (adjusted relapse rates: 50% vs. 59%, $p = .09$). The rates of relapse in the continuation ADM and placebo withdrawal conditions did not differ significantly (adjusted relapse rates: 53% vs. 59%, $p = .33$). This study also evaluated outcomes during an additional year of naturalistic follow-up similar to the design used by Hollon and colleagues (2005), and

they found a non-significant trend for prior psychotherapy versus prior continuation ADM (adjusted recurrence rates: CBT, 24%; BA, 26%; withdrawn from ADM, 52%).

Despite these promising data on the long-term efficacy of ADMs and CBT, there is a major limitation of the extant research. Specifically, the current evidence base is limited because most treatment studies end their follow-up period after one year (Borges et al., 2014; Cuijpers et al., 2013; Geddes et al., 2003; Glue et al., 2010). This is problematic since cumulative risk of recurrence increases beyond one year after treatment (Solomon et al., 2000), and practice guidelines recommend that clinicians make treatment decisions that could last beyond one year (APA, 2010; NICE, 2010). Further, because of appropriate *a priori* research design reasons, the few studies that have directly compared the long-term efficacy of CBT and continuation ADMs for longer than one year of follow-up (e.g., Dobson et al., 2008; Hollon et al., 2005) have, at the end of one year of treatment, withdrawn continuation ADM patients from treatment, rather than maintaining them on the effective ADM. Consequently, during the second year of follow-up these studies have used naturalistic designs, which involve fewer clinical contact hours and potentially limited treatment efficacy. Thus, there is a need for a study that allows patients to continue using ADMs through a second year of follow-up and to do so under continued and controlled clinical care. Such a design adds to the long-term outcome data for ADMs, the most common form of MDD treatment, and permits comparison of the long-term efficacy of CBT and maintenance ADMs beyond one year of follow-up.

The present study addressed these limitations in the literature with data from the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study (Dunlop et al., 2012; Dunlop et al., 2017). The PReDICT project was a multi-stage randomized controlled trial for the treatment of MDD in adults. The current analyses include those patients

who remitted to 12-week monotherapy (ADMs or CBT) and then participated in a 21-month follow-up in which they could continue their initial treatment (i.e., continued ADMs or up to 3 CBT booster sessions per year). The primary aim of the present study was to describe the rates of relapse and recurrence among these patients. Based on the highly-controlled nature of the study protocol and the inclusion of only patients who experienced the optimal initial treatment outcome (i.e., remission), it was expected that estimated rates of relapse and recurrence would be lower than reported in previous studies. In addition, it was expected that CBT with occasional booster sessions would have long-term efficacy that was comparable to continued treatment with ADMs.

Secondary Aims

Both the APA and NICE treatment guidelines recommend that clinicians assess a patient's risk of relapse and recurrence at the end of initial and continuation treatment (APA, 2010; NICE, 2010). To improve the assessment of patient risk, clinicians need to know which clinical variables reliably predict relapse and recurrence. Three such variables derived from prior relevant studies are: 1) prior number of depressive episodes at baseline; 3) baseline co-morbid anxiety; and 3) residual, subthreshold depression symptoms. These variables are cited as predictors of risk in the treatment guidelines (APA, 2010; NICE, 2010) and have also been cited in reviews of cross-sectional and longitudinal community studies (Burcusa & Iacono, 2007) and clinical cohort studies (Craighead & Dunlop, 2014; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). The secondary aim of the present study was to explore clinical variables that may predict MDD relapse and/or recurrence across treatment modalities. Specifically, it was hypothesized that residual symptoms, prior number of depressive episodes, and anxiety would differentiate patients who experienced a relapse or recurrence from those who did not.

Method

Study Overview

The PReDICT project was a randomized controlled trial aimed at identifying moderators of treatment response among patients who have never previously received treatment for Major Depressive Disorder (MDD). The study rationale, methods, and design have been described in detail elsewhere (for study protocol see: Dunlop et al., 2012). In brief, patients were randomized 1:1:1 to one of three 12-week monotherapies: 1) escitalopram (ESC; 10-20 mg/d), a selective serotonin reuptake inhibitor (SSRI); 2) duloxetine (DUL; 30-60 mg/d), a serotonin-norepinephrine reuptake inhibitor (SNRI); or 3) CBT; 16 one-hour individual sessions. Patients who remitted to their allocated 12-week monotherapy were eligible to enter a 21-month maintenance treatment period.

Participants

The present study included the PReDICT patients who remitted to 12-week monotherapy with no major protocol violations (n = 109) and agreed to participate in the 21-month follow-up (n = 94). Monotherapy remission was defined as a Hamilton Depression Rating Scale 17-item (HAM-D; Hamilton, 1967) score of ≤ 7 at both weeks 10 and 12 of monotherapy treatment. Outcomes from 12-week monotherapy have been described in detail in an earlier report (Dunlop et al., 2017).

All PReDICT study participants met DSM-IV-TR (APA, 2000) criteria for MDD and had a HAM-D score ≥18 at screening and ≥15 at their baseline visit. Exclusion criteria included prior treatment (lifetime) of a mood disorder (i.e., a marketed antidepressant at a minimum effective dose for 4 or more consecutive weeks or 4 or more sessions of an evidence-based and structured psychotherapy for depression); lifetime history of dementia, a primary psychotic

disorder, bipolar disorder, or a current diagnosis (i.e., within the past year) of obsessive-compulsive disorder, an eating disorder, or dissociative disorder. Participants were also excluded if they met criteria for substance abuse in the past 3 months or substance dependence during the 12 months prior to their first treatment visit.

All participants were assessed and treated under one umbrella clinic either at a university-affiliated outpatient setting or at a Spanish-speaking outpatient setting at a large public hospital. All participants provided written informed consent, and the Emory Institutional Review Board and the Grady Hospital Research Oversight Committee granted study approval. Trained clinicians and raters completed all interviews and assessments; data were gathered from participants during 2007-2015. The study was conducted in accordance with the Helsinki Declaration of 1975 and its amendments.

Procedure

Subjects who remitted to PReDICT 12-week monotherapy without a major protocol violation (e.g., using an unassigned treatment) and agreed to participate in follow-up (n = 94) were assessed every three months during the 21-month follow-up. These assessment visits consisted of a Longitudinal Interval Follow-up Evaluation (LIFE; Keller et al., 1987) interview by masked rater, a clinical interview with a psychiatrist, clinical ratings on the HAM-D (Hamilton, 1967) and Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) by a masked rater, and several self-report measures. Patients continued participating in follow-up until either: 1) 2 years from study baseline; 2) depressive relapse/recurrence; or 3) early termination or lost to follow-up. Participating patients received $50 per follow-up visit.

Patients who remitted to antidepressant monotherapy and agreed to participate in follow-up (ESC, n = 34; DUL, n = 37) were encouraged to remain on medication through the first nine

months of follow-up, when a study psychiatrist then discussed the risks and benefits of discontinuing medication. Patients could choose to maintain or stop medications; patients remained in the follow-up protocol for 12 more months regardless of their choice. Of the 60 ADM patients who survived the first nine months (12 months after baseline assessment) of follow-up without relapse/recurrence or attrition, 19 (31.7%) stopped their ADM before or at the month nine follow-up decision point. All antidepressant medications were managed in accordance with guidelines commonly used in depression treatment studies (Fawcett, Epstein, Fiester, Elkin, & Autry, 1987); clinical management sessions were limited to a maximum of 20 minutes during each quarterly visit. All physicians overseeing medication treatment were board-certified psychiatrists or fourth-year psychiatry residents under close supervision of the lead study psychiatrist (BWD).

Patients who remitted to CBT monotherapy and agreed to participate in follow-up (n = 23) were offered up to 3 booster sessions during the first 9 months of follow-up and up to three additional booster sessions during the second year of follow-up. All booster sessions were separated by at least 1 month, and an additional "crisis session" was also allowed for patients during each year of follow-up. CBT was delivered according to a standard CBT manual (Beck, Rush, Shaw, & Emery, 1979).

Measures

Depression severity and relapse/recurrence. The LIFE (Keller et al., 1987) is a semi-structured interview that tracks the exact dates of the onset and remission of psychiatric disorders, including MDD relapse/recurrence and time survived until relapse/recurrence. The LIFE has demonstrated high interrater reliability for episodic disorders (ICC = .90, Keller et al., 1987). The LIFE interview was conducted at the end of 12-week monotherapy treatment and at

each of 7 quarterly visits during the 21-month follow-up. The 17-item HAM-D (Hamilton, 1967; Williams, 1988) is a clinician-rated measure of depressive symptom severity over the past week and is one of the most commonly used measures in psychotherapy and antidepressant medication research. Patients were rated on the HAM-D throughout monotherapy treatment and at each follow-up visit.

Definition of relapse/recurrence. The present study follows other researchers (e.g., Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013) in referring to relapse and recurrence as the single construct of relapse/recurrence. The *a priori* definitions of relapse/recurrence used in PReDICT included a patient meeting any one of the four following criteria: 1) meeting criteria for a major depressive episode based on a LIFE score of 3 or greater; 2) a 17-item HAM-D $\geq$ 14 for two consecutive weeks (patients with an HAM-D $\geq$ 14 at a follow-up visit were asked to return the following week for an additional rating); 3) a 17-item HAM-D $\geq$ 14 at any follow-up visit and at which time the patient requested an immediate change in treatment; and 4) high risk of suicide, as determined by the study psychiatrist (Dunlop et al., 2012).

Residual symptoms. Residual symptoms were primarily operationalized as a patient's 17-item HAM-D symptom level at the end of 12-week monotherapy. Residual symptoms were also measured by patients' self-reported symptoms on the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) at the end 12-week monotherapy. The BDI is a widely-used measure of self-reported depressive symptoms over the past two weeks, and its psychometric properties have been evaluated extensively (Beck, Steer, & Carbin, 1988).

Prior number of depressive episodes. Prior number of episodes was based on data collected at PReDICT baseline via the Structured Clinical Interview for DSM-IV (SCID; First,

Spitzer, Gibbon, & Williams, 1998). Patients were categorized into two groups: patients with less than three prior depressive episodes, and patients with three or more prior episodes.

Anxiety. Anxiety was operationalized as a patient's anxiety disorder status (i.e., no/yes) as determined by the PReDICT baseline SCID. In addition, clinician ratings of patient anxiety severity on the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) at PReDICT baseline were used as an additional measure of anxiety.

Data Analysis

The following series of preliminary comparisons were performed using Chi-Square tests and Analysis of Variance (ANOVA) on the 7 demographic and 12 clinical variables listed in Table 1. First, eligible patients who agreed to participate in the present study were compared to eligible patients who did not agree to participate, and those patients who did not agree to participate were also compared across treatment groups. Second, to evaluate risk of differential retention of patients from the monotherapy phase to follow-up phase, treatment groups were compared at the beginning of the present study. Since differential retention of participants can affect group equivalence created by initial randomization (e.g., Klein, 1996), conservative p values ($p < .10$) were used for the treatment group comparisons per the method used in similar trials (e.g., Dobson et al., 2008; Hollon et al., 2005). Third, patients who left the study prior to the end of the 21-month follow-up were compared to all other participating patients (i.e., those who completed the 21-month follow-up and those who suffered a relapse/recurrence and were subsequently withdrawn from the study). In addition, patients who left the study were compared across treatment groups.

For the primary analyses, survival curves and times were estimated using the Kaplan-Meier product limit method (Kaplan & Meier, 1958), and the Mantel-Cox test was used to test

for differences across treatments (Mantel, 1966). For the analyses of the three clinical predictor variables, the Kaplan-Meier and Mantel-Cox methods were used to evaluate categorical variables, and the Cox proportional hazard regression model (Cox & Oakes, 1984; Kleinbaum & Klein, 2012) was used to evaluate continuous variables. In addition, Cox regressions were used to generate effect sizes (i.e., hazard ratios). Patient endpoints were defined as relapse/recurrence; patients lost to follow-up were right censored at the date of their final study visit, and patients who completed the entire follow-up protocol without relapse/recurrence were right-censored at 21-months after the end of monotherapy.

All analyses were conducted at a statistical significance of $p < .05$ (2-tailed), unless otherwise noted, and SPSS 24.0 and R 3.3.2 were used for the analyses. For all analyses including categorical variables, Fisher's exact test was substituted in analyses with small cells. Additionally, for some analyses, treatment conditions were collapsed to increase statistical power.

Results

Patient Flow and Attrition

One hundred and nine patients remitted to 12-week monotherapy without any major protocol violations and were eligible to participate in the present study. Fifteen of these patients did not participate in follow-up. Specifically, seven patients were not offered follow-up because that aspect of the study had not been initiated by the time they completed monotherapy; two patients refused to participate; and six patients consented but never returned. When compared to patients who agreed to participate ($n = 94$), these 15 non-participating patients were older (M_{age} = 43.9 vs. 38.1 years old), more likely to identify as Caucasian, and less likely to identify with the groups in the Other racial category (e.g., Asian, Native American, Central American). When the

7 patients who were not offered follow-up were excluded, the previous differences were no longer significant. Participation rates, adjusted for the 7 patients who were not offered follow-up, differed at the level of a non-significant trend among treatment groups (ESC, 100% (34/34); DUL, 90.2% (37/41); and CBT, 85.2% (23/27); Fisher's exact test, $p = .055$), and pair-wise comparisons revealed that ESC patients were significantly more likely to participate than CBT patients.

When evaluating the primary sample for this study, the 94 patients who agreed to participate, the treatment groups did not differ on any of 7 demographic or 12 clinical variables (see Table 1). Of participating patients, 21 **(**22.3%**)** left the study before suffering a relapse/recurrence or completing the entire 21-month follow-up protocol. Lastly, lost to follow-up rates did not differ among treatments (ESC, 29.4% (10/34); DUL, 24.3% (9/37); and CBT, 8.7% (2/23); X^2 (2) = 3.53, $p = .17$), although there was a nonsignificant trend when ADMs were collapsed into one group and compared to CBT (lost to follow-up rates: 26.8% vs. 8.7%; X^2 (1) = 3.27, $p = .07$).

The complete participant flow is summarized in Figure 1.

Sample Characteristics

Participants in the present study had a mean age of 38.1 years ($SD = 11.0$) and 50.0% were female. The participants' reported race was 48.9% Caucasian, 14.9% African American, and 36.2% Other. Reported ethnicity was 30.9% Hispanic and 69.1% Non-Hispanic. More than half of participants (57.4%) were married or cohabitating and 47.9% were employed full-time. Nearly one third of participants (33.0%) had a comorbid anxiety disorder at study entry, 28.7% had a history of more than 3 previous MDEs, and 29.0% had a chronic MDE (i.e., ≥ 2 years) at study entry. A complete description of the sample is provided in Table 1.

Prevention of Relapse/Recurrence

Only 13 patients suffered a relapse/recurrence (n = ESC, 3; DUL, 5; CBT, 5), and the survival curves for the entire 21-month follow-up period are presented in Figure 2. The Kaplan-Meier estimated rate of relapse/recurrence across all treatment conditions during this period was 15.5%, and the mean survival time was 77.7 weeks (95% CI [74.3, 81.1]). The estimated rates of relapse/recurrence for the treatment groups were: ESC, 10.6%; DUL, 15.7%; and CBT, 22.4%, and the mean survival times were: ESC, 80.7 weeks (95% CI [76.7, 84.7]); DUL, 78.7 weeks (95% CI [74.0, 83.3]; and CBT, 72.1 weeks (95% CI [62.7, 81.5]). The survival distributions did not statistically differ across treatment conditions (Mantel-Cox X^2 (2) = 1.74, p = .42), when the ADM conditions were collapsed into one group and compared with the CBT condition (estimated relapse/recurrence rates: 13.3% vs. 22.4%; Mantel-Cox X^2 (1) = 1.46, p = .23), or in any of the pair-wise comparisons.

An additional analysis evaluated patients who suffered a "relapse," defined as meeting relapse/recurrence criteria at or before the six-month follow-up visit (i.e., nine months from study baseline). Only three patients suffered a relapse during this time period (one in each treatment condition), and Kaplan-Meier estimates of the relapse rates across all treatment conditions was 3.2%. The estimated rates of relapse for the treatment groups were: ESC, 3.1%; DUL, 2.7%; and CBT, 4.3%, and the survival distributions did not statistically differ across any of the comparisons.

Due to the observed trend of higher "lost to follow-up rates" among ADM patients, a series of sensitivity analyses were completed (Shih, 2002). The first sensitivity analysis applied the estimated relapse/recurrence rates within each treatment group to the patients lost to follow-up. This assumption increased the number of relapse/recurrences by one in each of the ADM

conditions, and these additional relapses/recurrences were imputed at the average survival time of patients who suffered a relapse/recurrence within each condition (ESC, 51 weeks; DUL, 49 weeks). The second sensitivity analyses assumed that patients with elevated symptoms at their last assessment prior to dropping from the study suffered a relapse/recurrence at the time they dropped from the study. These analyses evaluated several symptoms thresholds (HAM-D ≥ 10, 11, or 12). Across all sensitivity analyses, the estimated combined rate of relapse/recurrence across treatment conditions ranged from 17.7% to 21.0%, and the estimated ranges in rates of relapse/recurrence for the treatment conditions were: ESC, 13.7% - 20.3%; DUL, 18.0% - 18.4%; and CBT, 22.4% - 27.0%.

Sustained Remission

Sustained remission rates were calculated as an additional measure of long-term treatment outcomes. Here sustained remission refers to the proportion of patients initially assigned to each treatment condition who remitted to 12-week monotherapy and then completed the entire 21-month follow-up protocol without a HAM-D rating ≥7 at any of the follow-up visits. Evaluating sustained remission rates has the benefit of considering treatment outcomes relative to the full, "intent-to-treat" sample and similar measures have been reported in comparable studies (e.g., Dobson et al., 2008; Hollon et al., 2005). The observed rate of sustained remission across all treatment conditions, adjusted for 26 patients who completed monotherapy prior to the initiation of the follow-up protocol, was 12.6% (40/318). The observed rates for the treatment groups were: ESC, 16.2% (17/105); DUL, 12.1% (13/106); and CBT, 9.4% (10/106). Rates of sustained remission were also calculated relative to the number of patients who agreed to participate in follow-up. Among these patients, the observed rate of sustained remission was 42.6%, and the observed rates for the treatment groups were: ESC,

50.0%; DUL, 35.1%; and CBT, 43.5%. Sustained remission rates did not statistically differ across any of the treatment comparisons. Exploratory analyses revealed that sustained remitters reported significantly lower baseline depression severity on the HAM-D ($F(1,316) = 14.62$, $p < .001$) and lower baseline anxiety on the HAM-A ($F(1,316) = 7.66$, $p = .006$).

Treatment Utilization

Over 70% (50/71) of participating ADM patients continued to use medications until the end of their participation in the study (i.e., relapse/recurrence, early termination, or study termination). Rates of relapse/recurrence did not statistically differ between patients who discontinued medication and patients who continued medications (observed relapse/recurrence rates: discontinued ADMs, 14.3% (3/18) vs. continued ADMs, 10.0% (5/45); Fisher's exact test, $p = .686$). Exploratory analyses revealed that patients who continued medications had higher baseline depression severity on the BDI ($M = 22.8$, $SD = 6.6$) than patients who discontinued medications (($M = 17.9$, $SD = 5.9$), $F(1,69) = 8.80$, $p = .004$).

All participating CBT patients (23/23) attended at least one booster session, and 21.7% (5/23) used a crisis session. Among the patients who completed the entire 21-month protocol (i.e., no attrition or relapse/recurrence), 43.8% used at or near their maximum number of allowed sessions (i.e., 5 or 6). Number of booster sessions attended, adjusted for survival time, was not associated with relapse/recurrence. Exploratory analyses revealed, however, that number of booster sessions attended was positively associated with baseline HAM-D scores ($r(23) = .58$, $p = .004$), BDI scores ($r(22) = .57$, $p = .006$), and HAM-A scores ($r(23) = .56$, $p = .006$).

Prediction of Relapse/Recurrence

Residual depressive symptoms on the HAM-D following monotherapy were evaluated via a Cox regression model. The analysis revealed that residual symptoms were associated with

increased risk in relapse/recurrence and decreased survival time (Hazard Ratio = 1.31, 95% CI [1.02., 1.67], Wald $X^2 = 4.41$, $p = .036$). Self-reported residual symptoms on the BDI, however, were not significantly associated with relapse/recurrence (Hazard Ratio = 1.07, 95% CI [.89, 1.30], Wald $X^2 = .53$, $p = .468$).

Patients were categorized by prior number of depressive episodes into two groups: patients with less than three prior episodes, and patients with three or more prior episodes. The observed relapse/recurrence rate for patients with fewer than three prior episodes was 11.9% (8/59), and the observed rate among patients with three or more prior episodes was 18.5% (5/27). The Kaplan-Meier estimated survival distributions did not statistically differ between groups (Mantel-Cox X^2 (1) = .69, $p = .408$), and prior number of depressive episodes was not associated with risk of relapse/recurrence (Hazard Ratio = .63, 95% CI [.21, 1.92], Wald $X^2 = .67$, $p = .412$).

Patients were divided into two groups based on anxiety disorder status (i.e., no/yes) at PReDICT baseline. The observed relapse/recurrence rate for patients without an anxiety disorder at study baseline was 7.9% (5/63), and the observed rate for patients with an anxiety disorder was 25.8% (8/31). The Kaplan-Meier estimated survival distributions differed significantly between the two groups (Mantel-Cox X^2 (1) = 4.80, $p = .029$), and not having an anxiety disorder at study baseline was associated with decreased risk of relapse/recurrence and longer survival times (Hazard Ratio = .31, 95% CI [.10, .94], Wald $X^2 = 4.28$, $p = .039$). However, anxiety symptoms on the HAM-A (a continuous variable) at study baseline were not associated with relapse/recurrence (Hazard Ratio = 1.01, 95% CI [.90., 1.13], Wald $X^2 = .03$, $p = .853$).

A multivariate model was constructed to simultaneously evaluate predictor variables from each clinical domain. The entered variables were HAM-D residual symptoms, a

categorical variable for anxiety disorder status at PReDICT baseline, and a categorical variable for prior number of depressive episodes. The overall model was significant (X^2 (2) = 8.80, p = .032), and two of the three predictor variables were marginally significant. Specifically, HAM-D residual symptoms were marginally associated with increased risk in relapse/recurrence and decreased survival time (Hazard Ratio = 1.29, 95% CI [.998, 1.670], Wald X^2 = 3.78, p = .052), and not having an anxiety disorder at study baseline was marginally associated with decreased risk of relapse/recurrence and longer survival times (Hazard Ratio = .33, 95% CI [.11, 1.04], Wald X^2 = 3.58, p = .059). Results from this model and the univariate analyses are summarized in Table 2.

Power Considerations

Ninety-four patients participated in the present study (*n:* ESC, 34; DUL, 37; CBT, 23), and 60 patients (*n:* ESC, 21; DUL, 23; CBT, 16) completed the entire 21-month follow-up protocol. Sensitivity analyses revealed that, depending on the comparison and frequency of participant attrition, the study was adequately powered to detect approximately .30 - .45 differences in relapse/recurrence rates.

Discussion

Results from the current analyses indicated that patients who remit to initial treatment and continue to receive maintenance treatment (i.e., continued ADMs or a modest number of CBT booster sessions) have a reduced risk of MDD relapse/recurrence. The relapse/recurrence rates were lower than the rates typically reported for patients followed naturalistically (e.g., Solomon et al., 2000) and for patients who respond to initial ADM treatment and then withdraw to placebo (Borges et al., 2014; Geddes et al., 2003; Glue et al., 2010). Moreover, the relapse/recurrence rates in the current study are lower than the rates reported in other large scale

trials with ADM and CBT treatment conditions (Dobson et al., 2008; Hollon et al., 2005; Jarrett et al., 2013; Klein et al., 2004; Shea et al., 1992).

One potential explanation for the low rates of relapse/recurrence in the current study is that most prior research followed patients who had *responded* to initial treatment, and the current study only followed patients who had *remitted*. Given the documented relationship between residual symptoms and relapse/recurrence (Judd et al., 1998; Paykel et al., 1995), it is reasonable to expect higher rates of relapse/recurrence among responders since they have more residual symptoms at the end of treatment when compared to remitted patients. Indeed, fully remitted patients have better long-term outcomes than patients who do not achieve full remission (Rush, Trivedi, et al., 2006). Another potential explanation is that the PReDICT study excluded patients who had received prior treatment. Patients with a history of failed treatment and patients who have previously responded to treatment but then relapsed may be pessimistic about additional treatment; both sets of circumstances attenuate treatment outcomes (Craighead & Dunlop, 2014).

The results from the current study show that controlled clinical care can reduce patient risk of relapse/recurrence for as long as 21 months of follow-up. This finding is important because the majority of treatment studies follow patients for less than one year (Borges et al., 2014; Cuijpers et al., 2013; Geddes et al., 2003; Glue et al., 2010). Moreover, this finding is relevant for clinicians who must make treatment decisions that have implications beyond one year after initial treatment (APA, 2010; NICE, 2010). Finally, if remission is a major driver of the low rates of relapse/recurrence in the current study, then these results support recommendations to make full remission the target of initial treatment (Keller, 2003).

In terms of relative treatment efficacy, the three conditions produced a low rate of relapse/recurrence; there were no statistically significant differences across conditions. This

result is consistent with arguments for the comparable efficacy of initial CBT vs. acute ADMs plus continued ADMs (Cuijpers et al., 2013; Hollon, Stewart, & Strunk, 2006), although additional data are needed. If ADMs and CBT do have comparable long-term efficacy, it is possible that they work through different mechanisms (McGrath et al., 2013). For instance, CBT may teach patients regulation skills to downregulate negative emotional states, and ADMs may improve functioning in dysregulated neurocircuitry (Dunlop & Mayberg, 2014). These results provide much-needed long-term follow-up data on the comparative efficacy of CBT and ADMs and come from one of the first studies to maintain ADM patients on treatment throughout follow-up.

The current study also found that residual symptoms on the HAM-D, both on its own and after controlling for other predictor variables, predicted relapse/recurrence. This finding is consistent with the aforementioned evidence for residual symptoms predicting relapse/recurrence (Judd et al., 1998; Paykel et al., 1995) and with findings from the STAR*D trial that residual symptoms predicted relapse/recurrence among remitters to initial treatment (Nierenberg et al., 2010). Residual symptoms may predict relapse/recurrence because they indicate that patients are still suffering from the index depressive episode, making them more vulnerable to relapse (Judd et al., 2016). This finding has important implications for treatment since many patients end initial treatment with residual symptoms (DeRubeis et al., 2005; Dimidjian et al., 2006; Dunlop et al., 2017; Elkin et al., 1989; Keller et al., 2000). Moreover, evidence that residual symptoms predict relapse/recurrence even among remitters supports recent efforts to define more stringent MDD outcome criteria (Dunlop, Holland, Bao, Ninan, & Keller, 2012; Judd et al., 2016).

Although the current study found that HAM-D residual symptoms predicted relapse/recurrence, it also found that residual symptoms on the BDI did not. Some trials have

reported conflicting results across depression symptom measures (Iovieno, van Nieuwenhuizen, Clain, Baer, & Nierenberg, 2011; Nierenberg et al., 2010), and other studies have reported consistent results across measures (ten Doesschate, Bockting, Koeter, & Schene, 2010). The divergent findings in the current study could reflect differences in symptoms assessed by the HAM-D and BDI (Brown, Schulberg, & Madonia, 1995; Shafer, 2006), or a restriction of range in residual symptoms due to the inclusion of only remitters. Regardless of the explanation, a patient's level of residual symptoms is one of the most robust clinical predictors of MDD relapse/recurrence (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010; Judd et al., 2016), and the current study supports this claim.

The current study also found that an anxiety disorder diagnosis at study baseline, both on its own and after controlling for other predictor variables, predicted relapse/recurrence. This is consistent with evidence from longitudinal studies that have also found a relationship between anxiety disorder diagnoses and MDD relapse/recurrence (Coryell, Endicott, & Keller, 1991; Rao, Hammen, & Daley, 1999; Wilhelm, Parker, Dewhurst-Savellis, & Asghari, 1999). Patients with a comorbid anxiety disorder may suffer from greater exposure to an underlying vulnerability factor than patients without comorbid anxiety. For example, these patients may rely on emotion regulation strategies like rumination and avoidance that put them at risk for emotional disorders (Barlow, Allen, & Choate, 2004; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). This finding is clinically relevant because of the significant comorbidity of depression and anxiety (Kessler et al., 2005; Trivedi et al., 2006). This finding also suggests the need for modified treatments that differentially target factors that maintain anxiety and depression.

Even though anxiety disorder diagnoses at study baseline predicted relapse/recurrence in the current study, baseline anxiety symptom severity on the HAM-A did not. This finding

differs from results from a recent study that found that anxiety symptom severity predicted relapse/recurrence in the CBT condition and that an anxiety disorder diagnosis did not predict relapse/recurrence in any of the treatment conditions (Forand & DeRubeis, 2013). Moreover, there is evidence that anxiety symptom severity predicts relapse/recurrence over and above residual depressive symptoms (Coryell et al., 2012) and that "anxious depression" symptoms predicts poorer treatment outcomes (Farabaugh et al., 2012; Fava et al., 2008). One potential explanation for the results in the current study is the use of the HAM-A as a measure of anxiety symptoms. Studies that have found a relationship between anxiety symptoms and relapse/recurrence have generally used other measures (Coryell et al., 2012; Forand & DeRubeis, 2013). In addition, the HAM-A has been criticized for tapping aspects of depression and missing aspects of anxiety (Koerner, Antony, & Dugas, 2010; Maier, Buller, Philipp, & Heuser, 1988). Despite these discrepancies in the literature, there is accumulating evidence that comorbid anxiety likely impacts depression treatment outcomes and that there may be a need for more specialized treatments for those with comorbid anxiety and depression.

Finally, the current study did not find that prior number of MDEs predicted relapse/recurrence. Numerous studies have found that patients with more prior depressive episodes are at increased risk of relapse/recurrence (Bulloch, Williams, Lavorato, & Patten, 2014; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Mueller et al., 1999), and prior MDEs have been found to moderate treatment outcomes to psychotherapies that specifically target the prevention of MDD relapse/recurrence (e.g., Bockting et al., 2005; Teasdale et al., 2000). Given these discrepancies, it is possible that the current study may not have been sufficiently powered to detect the difference in risk between patients with more than three prior episodes and patients with fewer than three prior episodes. The more plausible interpretation is that the current sample

were treatment naïve, suggesting that their prior episodes may have had lesser detrimental effects on future functioning. Consistent with this conclusion, the sample in the current study may have had relatively fewer patients with highly recurrent depression (i.e., more than three prior episodes), which could have limited the magnitude of the expected effect.

Limitations

There are several limitations to the current study. First, a key limitation of any follow-up study is the risk of differential retention of patients (Klein, 1996). For the current study, less than thirty percent of patients initially randomized to treatment were eligible (i.e., remitted to monotherapy) and participated in follow-up. Moreover, although analyses did not detect differences in participants across treatment groups at the start of follow-up, differing lost to follow-up rates could have biased treatment comparisons. However, lost to follow-up rates in the current study were comparable to those observed in similar studies, and sensitivity analyses were used to account for this risk. Second, although the sample size in the current study was comparable to that of similar trials, the current study lacked statistical power to detect small to moderate, yet clinically significant, effects between treatments conditions.

Third, the study sample was treatment naïve, which may limit the study's generalizability to individuals who are depressed and have failed prior treatments. It is worth noting, however, that results from the monotherapy phase of the PReDICT study were similar to those of other depression treatment studies (Dunlop et al., 2017), suggesting that treatment efficacy may be comparable between treatment naïve and non-naïve patients. Fourth, patients could choose to end continuation treatment during follow-up, which might have introduced unsystematic change into the study. Most patients, however, continued treatment, and continuing treatment was positively associated with symptom severity. Finally, the clinical care in the current study was

provided in an academic medical setting by highly-trained, experienced clinicians and most of the patients were recruited by advertisements of the study. This setting differs from how mental health care is generally sought and delivered (Westen, Novotny, & Thompson-Brenner, 2004), and may limit generalizability.

Future Research

The current study obtained low rates of relapse/recurrence among patients who remitted to monotherapy and received systematic evaluation and treatment for up to two years. Additional research is needed to replicate these findings with a treatment naïve sample, to provide additional estimates of relative treatment efficacy between CBT and ADMs, and to synthesize results from multiple studies. Future research would benefit from also investigating the role of initial treatment outcomes, such as response and remission, in differentiating long-term outcomes, and from including a length of follow-up sufficient to incorporate MDD recurrence (i.e., more than one year of follow-up). Perhaps the most valuable research direction would be evaluation of biomarkers that differentiate those who sustain positive treatment outcomes from those who have a relapse/recurrence; such data might provide stronger predictors of outcomes and provide clarity of the mechanisms of relapse/recurrence and the relationship of biomarkers to clinical predictors.

Conclusion

The estimated relapse/recurrence rates in the current study support the benefits of continued clinical care (i.e., continuation ADMs or CBT booster sessions) among patients who remit to initial monotherapy treatment. These benefits were observed for patients treated with ESC, DUL, or CBT. Results from the clinical predictor analyses indicate that residual depressive symptoms after initial successful treatment and a comorbid anxiety disorder diagnosis

at study baseline each predict poorer long-term clinical outcomes. This finding may imply the need for more specialized forms of treatment for patients with these risk factors. Overall, results from the current study suggest that for previously untreated patients who remit with a monotherapy intervention, treatment provides protection against relapse/recurrence for at least two years for the great majority of patients.

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Table 1.

Demographic and clinical characteristics of participants

Characteristic	All Patients (N = 94)		CBT (*n* = 23)		ESC (*n* = 34)		DUL (*n* = 37)			
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	F	*p*
Age (yrs)	38.1	11.0	36.7	10.7	38.6	10.2	38.6	12.1	0.26	0.780
Age at first episode (yrs)	29.0	12.7	30.3	11.5	31.2	13.2	26.1	12.6	1.63	0.202
Current episode duration (wks)	105.4	191.8	72.5	73.8	113.6	187.6	118.7	243.1	0.45	0.639
Baseline HAM-D	18.6	3.5	18.5	3.3	18.9	3.9	18.2	3.2	0.38	0.686
Baseline BDI	21.6	6.9	22.4	7.6	21.1	6.9	21.5	6.7	0.22	0.807
Baseline HAM-A	14.4	4.7	15.1	4.8	15.0	4.9	13.4	4.4	1.36	0.261
Week 12 HAM-D	2.8	2.2	2.7	2.3	2.4	2.0	3.2	2.2	1.35	0.264
Week 12 BDI	2.1	2.5	2.8	2.9	1.4	2.1	2.3	2.5	2.13	0.125
	n	%	*n*	%	*n*	%	*n*	%	X^2	*p*
Sex									0.07	0.965
Male	47	50.0	11	47.8	17	50.0	19	51.4		
Female	47	50.0	12	52.2	17	50.0	18	48.6		
Race									5.94	0.201
Caucasian	46	48.9	15	65.2	16	47.1	15	40.5		
Black	14	14.9	1	4.3	4	11.8	9	24.3		
Other	34	36.2	7	20.4	16	47.1	13	35.1		
Ethnicity									0.57	0.752
Hispanic	29	30.9	7	30.4	12	35.3	10	27.0		
Non-Hispanic	65	69.1	16	69.6	22	64.7	27	73.0		
Married/Cohabitating									2.16	0.340
Yes	54	57.4	16	69.6	17	50.0	21	56.8		
No	40	42.6	7	30.4	17	50.0	16	43.2		
Employed full-time									2.07	0.356
Yes	45	47.9	14	60.9	15	44.1	16	43.2		
No	49	52.1	9	39.1	19	55.9	21	56.8		
Anxiety disorder at baseline									0.31	0.858
Yes	31	33.0	8	34.8	10	29.4	13	35.1		
No	63	67.0	15	65.2	24	70.6	24	64.9		
Previous episodes									3.97	0.410
1	47	50.0	13	56.5	20	58.8	14	37.8		
2	20	21.3	5	21.7	6	17.6	9	24.3		
≥3	27	28.7	5	21.7	8	23.5	14	37.8		
Chronic episode (≥ 2 yrs)	27	29.0	7	30.4	9	26.5	11	30.6	0.17	0.918
History of suicide attempt	6	6.4	0	0.0	2	5.9	4	10.8	2.41	0.279
Insurance status									1.04	0.594
Yes	44	47.3	13	56.5	15	44.1	16	44.4		
No	49	52.7	10	43.5	19	55.9	20	55.6		

Table 2.

Univariate and multivariate Cox regressions predicting depressive relapse/recurrence

Univariate Models

Variables	Parameter Estimate	SE	Wald X^2	*p*	Hazard Ratio [95% CI]
Residual Symptoms					
HAM-D	0.27	0.13	4.41	0.036	1.31 [1.02, 1.67]
BDI	0.07	0.10	0.53	0.468	1.07 [.89, 1.30]
Prior Depressive Episodes					
<3 vs. ≥3 prior MDEs	-0.47	0.57	0.67	0.412	.63 [.21, 1.92]
Baseline Anxiety					
HAM-A	0.01	0.06	0.03	0.853	1.01 [.90, 1.13]
Anxiety Disorder Status	-1.18	0.57	4.28	0.039	.31 [.10, .94]

Multivariate Model

Variables	Parameter Estimate	SE	Wald X^2	*p*	Hazard Ratio [95% CI]
HAM-D Residual Symptoms	0.26	0.13	3.78	0.052	1.29 [1.00, 1.67]
<3 vs. ≥3 prior MDEs	0.01	0.59	0.00	0.991	1.01 [.32, 3.22]
Anxiety Disorder Status	-1.11	0.59	3.58	0.059	.33 [.11, 1.04]

Figure 1.

CONSORT flow chart

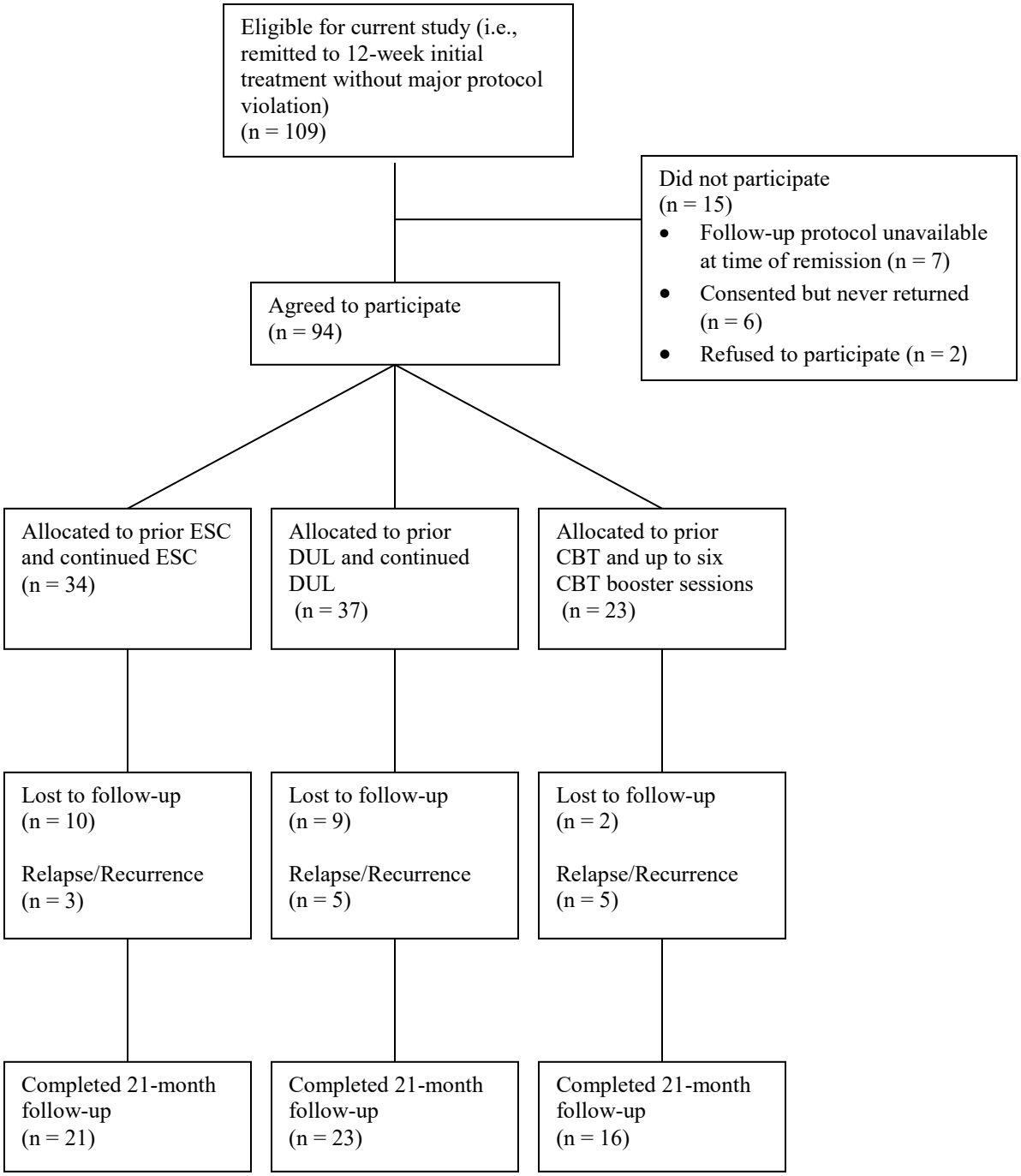

Figure 2.

Cumulative proportion of participants surviving without depressive relapse/recurrence over 21 months of follow-up