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8 **Cognitive Therapy vs. Antidepressant Medications in the Treatment of Depressed**
9 **Patients with and without Personality Disorder**

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28 **Running Head:** Personality Disorders and Treatment

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30 Abstract

31 **Context:** Conflicting evidence exists regarding the effect of comorbid personality
32 pathology in the treatment of depression.

33 **Objective:** To analyze attrition, response to treatment, and relapse in patients with and
34 without personality disorder in data from a randomized controlled trial of cognitive
35 therapy versus antidepressant medication.

36 **Design:** Random assignment to 16 weeks of medications (n=120) or cognitive therapy
37 (n=60), or 8 weeks of placebo (n=60). At 16 weeks, medication responders were
38 randomly assigned to continuation medication or placebo and compared to cognitive
39 therapy responders over a 12-month follow-up period.

40 **Settings:** Clinics at the University of Pennsylvania and Vanderbilt University.

41 **Patients:** 120 outpatients with moderate-to-severe Major Depressive Disorder.

42 **Interventions:** Paroxetine, up to 50 milligrams daily, augmented if necessary with
43 lithium or desipramine; individual cognitive therapy.

44 **Main Outcome Measure:** The Hamilton Rating Scale for Depression

45 **Results:** There was a significant personality-disorder-status by treatment interaction at
46 16- weeks. For patients with personality disorder, 61% responded to medications versus
47 44% to cognitive therapy; for those without personality disorder, 70% responded to
48 cognitive therapy versus 49% to medications. There was also a personality-disorder-
49 status by treatment interaction on the percentage of patients who both achieved response
50 and sustained it throughout the 12-month follow-up. In the personality-disordered group,
51 rates were 38% for prior cognitive therapy, 38% for continued medications, and 6% for
52 patients withdrawn from medications. In the non-personality disordered group, rates were

53 43% for prior cognitive therapy, 23% for medication withdrawal, and 21% for continued
54 medications.

55 **Conclusion:** Patients with comorbid personality disorders responded better to
56 medications than to cognitive therapy; the reverse was true for patients without
57 personality disorders. After 12 months, patients with personality disorders were equally
58 likely to have evidenced a sustained response with either continued medications or prior
59 cognitive therapy, and more likely than patients who were begun on medications and
60 switched to placebo.

61 Personality Disorders and Treatment Outcome in Moderate to Severe Depression

62

63 There is little agreement about the degree to which comorbid personality
64 pathology affects response to treatments for depression. Indeed, findings from two recent
65 meta-analyses generated two conflicting conclusions.^{1,2} One reported that depressed
66 patients with comorbid personality disorders (PD), relative to those without a diagnosed
67 personality disorder (Non-PD), experienced poorer response to treatment across all
68 treatment modalities and study designs.¹ Authors of the other meta-analysis focused only
69 on a small sample of high quality randomized controlled trials (RCTs) of
70 pharmacological treatments and found no such relation.² One reason for the disparity in
71 these results no doubt stems from differences in the strictness of the criteria for
72 methodological rigor employed in the two reviews. A widely-held assumption,³
73 questioned by some,⁴ is that the more rigorous the study, the less likely it is to yield
74 differential treatment outcomes for patients with and without PDs. The present study
75 attempts to add to this debate by asking whether comorbid PD diagnoses affect response
76 to treatment, and relapse following treatment, in a multi-site, randomized controlled trial
77 comparing cognitive therapy and antidepressant medication.

78 Treatment guidelines from the American Psychiatric Association state that
79 “cognitive behavioral therapy may be more effective than other treatments for depressed
80 individuals with personality disorders.”⁵ As Hollon and colleagues have noted, however,
81 this statement is based largely on a misunderstanding of data from the Treatment of
82 Depression Collaborative Research Program (TDCRP) sample.^{6,7} The TDCRP did not
83 reveal a significant PD-status-by-treatment interaction, the statistical finding that most
84 clearly could substantiate such a claim. Rather, a nonsignificant trend emerged whereby

85 Non-PD patients responded more poorly than did PD patients in the CT condition. If one
86 examines outcomes across treatment conditions, however, there was no evidence that PD
87 patients responded better to CT than to any other treatment, and there was no effect of PD
88 status in any of the other treatment conditions.⁸ Furthermore, results from subsequent
89 studies have not supported the claim that the presence of PD predicts favorable response
90 to CT.^{9, 10}

91 This misunderstanding may be due, in part, to the tendency in prediction analyses
92 to focus on whether comorbid PD predicts poor treatment response within a given
93 treatment modality. The more important issue, however, is whether two or more
94 treatments differ in their effectiveness with these patients, or in the complementary
95 group, patients without PD. To examine this question, we present findings regarding Axis
96 II comorbidity and the prediction of treatment outcome and subsequent relapse. Data are
97 drawn from a large, multi-site randomized controlled trial comparing CT and paroxetine
98 for individuals diagnosed with moderate-to-severe depression.^{11, 12} We focus on whether
99 PD status might be used prescriptively by asking whether the diagnosis of a comorbid PD
100 predicts differential response to CT versus pharmacotherapy, and we explore the effects
101 of PD on relapse rates once treatment is terminated.

102 Patients and Methods

103 The sample characteristics, treatment protocols, and main treatment outcome
104 findings have been reported elsewhere.^{11, 12} Briefly, the sample consisted of 180
105 depressed outpatients (measured using the Structured Clinical Interview for DSM-IV
106 Diagnosis¹³) who registered a score of 20 or higher on the modified 17-item version of
107 the Hamilton Rating Scale for Depression.¹⁴ PD diagnosis were made at intake using the

108 Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II).¹⁵ Among
109 the entire sample, 48% of individuals met criteria for at least one comorbid personality
110 disorder, and 8% met criteria for more than one. Patients with antisocial, borderline, or
111 schizotypal PD were excluded. Cluster A and B disorders were each diagnosed in
112 approximately 3% of the sample, 30% were diagnosed with cluster C PDs, and 14% met
113 criteria for PD not-otherwise-specified (PD-NOS). As Table 1 shows, the distribution of
114 personality disorders was quite similar between the treatment conditions. Note that PD-
115 NOS was the single most frequently diagnosed personality disorder. In order to determine
116 the nature of the overall relation of PD to outcome detailed below, for follow-up
117 analyses, these patients were reclassified into the PD category for which they reported the
118 highest concentration of symptoms.

119 *Treatments*

120 Prior to entering the acute phase of the trial, patients were randomly assigned to
121 receive cognitive therapy (CT, N = 60), antidepressant medication treatment with
122 paroxetine (ADM, N=120), or pill-placebo (N = 60). After 8 weeks of the 16-week acute
123 treatment phase, the placebo arm was terminated and patients who had been receiving
124 placebo were offered treatment at no cost. Patients receiving ADM were continued on
125 paroxetine at their established dose; for patients who did not meet pre-established
126 response criteria at 8 weeks (described below), augmentation with lithium or desipramine
127 was initiated. At the end of 16 weeks, half of the responders from the ADM group were
128 randomly assigned to be withdrawn from medication onto pill placebo (cP-P) while the
129 other half were continued on a maintenance dose (cADM) throughout the one-year
130 continuation phase.

131 CT was provided by 6 therapists, 2 male and 1 female at each of the two sites, the
132 University of Pennsylvania and Vanderbilt University. ADM treatment was provided by
133 3 board-certified psychiatrists at the Penn site and 2 at the Vanderbilt site, all of whom
134 were male. The characteristics and training of these treatment providers are detailed
135 elsewhere.¹¹ All assessments were conducted by independent evaluators who were blind
136 to treatment condition. When ADM patients were randomized to cP-P or cADM at the
137 beginning of the continuation phase, the process was triple blind – neither patients,
138 pharmacotherapists, nor evaluators knew which patients were receiving active
139 substances.

140 The criterion for response at 8 weeks was an HRSD score of 12 or lower, with the
141 last observation carried forward for patients who dropped out of treatment. At 16 weeks,
142 the response criterion was similarly anchored on an HRSD score of 12 or lower.
143 However, in order to limit the effect of transient mood fluctuations on the response
144 designation, additional constraints required patients to have scored 14 or less at week 14,
145 or 12 or less at weeks 10 and 12. Patients who scored higher than 12 at week 16 were still
146 considered responders if they had scored 12 or below at weeks 12 and 14, as well as at an
147 additional evaluation at 18 weeks. Response at 16 weeks also required the completion of
148 acute treatment.

149 Of the 180 patients assigned to ADM or CT, 104 patients met the response criteria
150 at 16 weeks and were entered into the 12-month continuation phase of the study. As
151 mentioned above, responders in the ADM condition were randomly assigned to a
152 continuation medication condition (n=34) or withdrawal onto pill-placebo (n=35). For
153 patients who were continued on active medications, their dose and augmentation

154 regimens were continued throughout this phase. For patients withdrawn onto placebo,
155 “dose” and “augmentation” adjustments were similarly allowed. However, the patient
156 received no active psychotropic medication of any kind. Plasma levels were fabricated
157 for patients who were receiving placebo lithium.

158 In the CT condition, regular therapeutic contact ceased at the end of the acute
159 phase of treatment. Treatment responders (N=35) could use up to 3 one-hour booster
160 sessions throughout the one-year continuation phase. All patients, regardless of their
161 treatment condition, were asked not to engage in ad-hoc treatment for depression, and all
162 were monitored closely throughout follow-up to assess the re-emergence of symptoms.

163 *Outcome Measures*

164 The primary outcome measure was the 17-item version of the HRSD. During the
165 acute phase, assessments with evaluators blind to treatment condition were held weekly
166 for the first four weeks and biweekly from week 6 to week 16. During the continuation
167 phase, assessments were conducted during each of the first two weeks, biweekly through
168 the end of the second month, and monthly thereafter. Relapse was defined as score of 14
169 or greater on the HRSD during two consecutive weeks (ad hoc assessments were
170 scheduled as needed to confirm this temporal component). In the event of missing data,
171 relapse could be also judged to have occurred using the Longitudinal Interval Follow-up
172 Evaluation.¹⁶

173 *Statistical Analyses*

174 The primary statistical analyses addressed the question of whether there were
175 differences in efficacy between the two active treatments as a function of PD-status, by
176 examining: a) the percent of patients meeting response criteria, b) the rate of symptom

177 reduction, and c) the percent who met response criteria and did not relapse post-
178 treatment. In all three sets of analyses, the treatment-by-PD-status interaction term was of
179 primary interest. In addition to these 3 primary analyses, follow-up analyses were
180 performed, when appropriate, to reveal which specific PD diagnoses were driving any
181 observed effects.

182 For the acute phase data, Cochran-Mantel-Haenszel (CMH) tests were used to
183 assess differential response/nonresponse as a function of treatment and personality
184 disorder status. This test extends the Chi-square statistic from a test of the association of
185 items within a contingency table to assess the association of sets of contingency tables.¹⁷
186 Interaction effects were tested using a logistic regression model based on the Likelihood
187 Ratio Chi-square statistic.¹⁸ Continuous data were examined with hierarchical linear
188 modeling (HLM) and multiple regression techniques. The HLM approach adjusts for
189 repeated measures with nested random effects.^{19,20} Using this approach, each subject's
190 growth curve is estimated from a collection of patient-specific parameters. Within-subject
191 level and between-subjects level effects are combined to form a mixed linear model with
192 both fixed and random coefficients. For all analyses reported, an unstructured covariance
193 structure was assumed. Two baseline scores were obtained for all participants, allowing
194 for a full intent-to-treat analysis while at the same time covarying for each patient's initial
195 baseline depression severity score. All models were performed using SAS Version 9.0,
196 PROC MIXED for HLM analyses, PROC FREQ for CMH tests, and PROC GENMOD
197 for Logistic Regression (SAS Institute Inc, Cary, NC).

198 One of the advantages of HLM analyses for repeated data is that they do not
199 require complete data from each subject. One drawback, however, is that differential

200 attrition rates can, in some circumstances, lead to misleading slope estimates.^{21, 22} This
201 problem may be compounded when the crucial assumption of linearity is violated, as is
202 almost invariably the case with rates of symptom reduction in outcome studies of
203 treatments for depression.²³ Because HLM analyses calculate the estimate of an
204 individual's parameters by adjusting for the behavior of the nested group to which that
205 individual belongs, the earlier a participant drops out, all else equal, the more closely that
206 individual's parameter estimates will approximate that of their group. In addition, given
207 the tendency for early symptom change to be steeper than later change, individuals who
208 drop out early might inappropriately influence the slope estimate of their group. Although
209 a patient who drops out early will have less influence on the slope estimate of her group
210 than will other patients who contribute more data, when groups differ on the number of
211 early treatment dropouts, these small effects can accumulate to artificially increase the
212 magnitude of the slope estimate and make it appear as if the group experienced change at
213 an increased rate. Because trend level differences emerged regarding dropout (see
214 attrition analyses below), a multiple regression analysis using a last observation carried
215 forward (LOCF) approach was performed as a check on this potential source of bias.
216 Models using these values err on the opposite side of the issue, relative to the errors that
217 can occur in an HLM, by assuming that a patient who drops out would not have
218 continued to change had he/she remained in treatment.

219 The Cox Proportional Hazards Model was used to estimate both dropout and
220 relapse rates.²⁴ Because a differential response rate for PD and Non-PD patients emerged
221 between the two treatments (see below), the Cox Proportional Hazards technique is
222 inappropriate on its own to estimate survival rates during the continuation phase. Any

223 indication of differential relapse might be an artifact of a differential sieve through which
224 the difficult-to-treat patients already failed to respond to a particular treatment, and
225 therefore did not enter the continuation phase.²⁵ To address this concern, Cox
226 Proportional Hazards regression was used to estimate the survival curves during the 12-
227 month continuation. These values were then weighted by the proportion of patients who
228 responded to treatment in each condition in order to estimate the percentage of patients
229 who continued to meet response criteria at the conclusion of the study. In the original
230 publication, 4 possibly confounding covariates (dysthymia, atypical depression subtype,
231 number of prior episodes, and gender) were entered in the survival analyses.¹² These 4
232 covariates were included in the present analyses as well. Cox Proportional Hazard
233 regression models were fit in the SAS procedure, PROC PHREG.

234 Results

235 *Attrition*

236 The overall rate of patient attrition was detailed in the original publication.¹¹
237 Although survival analyses revealed no overall difference between the PD and Non-PD
238 groups ($\chi^2(1) = 0.32, p = .57$), a statistically non-significant trend level PD-status-by-
239 treatment interaction did emerge ($\chi^2(1) = 2.72, p < .10$). This effect was driven in large
240 part by the fact that the dropout rate was lower for PD (12%) than for Non-PD (21%)
241 patients in the ADM condition and lower for Non-PD patients (12%) than for PD (22%)
242 patients in the CT condition.

243 *Outcome of Acute Treatment*

244 Categorical Response Analyses at 16 Weeks. There was a significant interaction
245 between treatment condition and personality disorder status in acute treatment response

246 ($\chi^2(1) = 6.77, p = .009$). As displayed by the narrow bars in the figure, in the PD group
247 there was a non-significant trend in favor of ADM, $66 \pm 12\%$ met response criteria
248 compared to $44 \pm 19\%$ in the CT condition (CMH $\chi^2(1) = 3.42, p = .06$, Odds Ratio = 2.37,
249 95% CI: 0.96--6.18). The reverse pattern was found for the Non-PD group, with $70 \pm 16\%$
250 meeting response criteria in the CT condition, compared to $49 \pm 13\%$ in ADM (CMH χ^2
251 $(1) = 3.20, p = .07$, OR = 2.26, 95% CI: 0.92--5.54). The test of the three way site-by-
252 treatment-by-PD-status interaction was not significant ($\chi^2(1) = .08, p = .77$), nor were the
253 main effects of treatment ($\chi^2(1) < .01, p = .97$) or PD status ($\chi^2(1) = .43, p = .51$).
254 Looking within treatments, the effect of PD-status was not significant in the ADM
255 condition (CMH $\chi^2(1) = 2.03, p = .15$, OR = 1.75, 95% CI: 0.81--3.74); there was,
256 however, a non-significant trend in favor of the Non-PD group in the CT condition
257 (CMH $\chi^2(1) = 3.71, p = .054$, OR = 2.85, 95% CI: 0.98--8.25).

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A similar pattern was observed at the end of 8 weeks and appeared to be
263 accounted for by the superior effect of the active treatments compared to placebo in each
264 of the two groups. Among patients in the PD group, ADM was superior to placebo (CMH
265 $\chi^2(1) = 4.43, p = .04$, OR = 2.7, 95% CI: 1.06--6.87) whereas CT was not (CMH $\chi^2(1)$
266 $= 0.06, p = .81$, OR = 1.15, 95% CI: .38--3.54). There was a non-significant trend in favor
267 of ADM over CT in this group (CMH $\chi^2(1) = 2.96, p = .09$, OR = 2.28, 95% CI: .88--
268 5.90). For patients in the Non-PD group, both active treatments were superior to placebo
269 (CMH $\chi^2(1) = 5.47, p = .02$, OR = 3.33, 95% CI: 1.19--9.35 for ADM; and CMH $\chi^2(1) =$

270 6.83, $p = .009$, OR = 4.47, 95% CI:1.41--14.12 for CT). There was no difference between
271 CT and ADM in this group (CMH $\chi^2(1) = 0.30$, $p = .58$, OR = 1.27, 95% CI:.54—2.99 in
272 favor of CT).

273 Continuous Response Analyses at 16 Weeks. In the original publication of the
274 treatment outcome data, the authors reported a significant site-by-treatment interaction in
275 the HLM analyses.¹¹ Therefore this interaction was added to all of the models described
276 below. The test of the treatment-by-PD-status interaction on the linear rate of symptom
277 change was not significant ($F(1, 171) = 1.97$, $p = .16$, Cohen's $d = .40 \pm .44$, the
278 confidence interval is the average of the estimates, calculated using Bird's formula, for
279 the PD and Non-PD groups²⁶).

280 For the LOCF analyses, all independent terms were centered around the grand
281 mean. The treatment-by-PD status interaction in this model was significant ($F(1, 173) =$
282 4.18 , $p = .04$). Neither the main effect of treatment ($F(1, 173) = .05$, $p = .82$), PD status
283 ($F(1, 173) = .26$, $p = .61$), nor the three-way site-by-treatment-by-PD-status interaction
284 ($F(1, 171) = .14$, $p = .71$) reached significance. The treatment effect did not reach
285 significance in either group ($F(1, 173) = 2.42$, $p = .12$ for the PD group; $F(1, 173) = 1.83$,
286 $p = .18$ for the Non-PD group). For the patients with PDs, the Cohen's d type effect size
287 was $.36 \pm .46$ in favor of ADM, relative to CT. For the Non-PD group, Cohen's d was $.29$
288 $\pm .43$ in favor of CT. A similar pattern was found for patients who dropped out of
289 treatment, although none of the effects noted in the following is significant (all t s < 1.7 ,
290 p s $> .10$). At the time of dropout, the least-squares mean estimates of HRSD scores for
291 patients in the PD group was higher in the CT condition ($M = 18.6$, $SD = 5.4$), relative to
292 the ADM ($M = 17.1$, $SD = 6.3$) condition (Cohen's $d = .24 \pm 1.09$). For patients in the

293 Non-PD group, mean HRSD scores were higher in ADM ($M = 22.2$, $SD = 5.9$) than in CT
294 ($M = 15.6$, $SD = 12.3$; Cohen's $d = .68 \pm 1.12$).

295 *Individual Personality Disorder Diagnoses*

296 The results reported thus far were achieved by grouping together all patients with
297 at least one PD diagnosis. In order to better determine what was driving the observed
298 effects, we further analyzed the data to characterize the relations for individual
299 personality disorders. As can be seen in Table 1, however, only 3 of the original
300 personality disorder diagnoses (Avoidant PD, Obsessive-Compulsive PD, and PD NOS)
301 and 1 of the PD clusters (Cluster C) were represented sufficiently in both treatments to
302 warrant further exploration. Of these 4 possible groupings, only the PD-NOS group
303 showed a significant superiority of the ADM over the CT condition in the response to
304 acute treatment ($CMH \chi^2(1) = 3.86$, $p < .05$, $OR = 5.63$, 95% CI: 0.97--32.66). Although
305 the treatment effect did not reach significance in the remaining 3 groups (all $ps > .15$), the
306 point estimates of the odds ratios favored the ADM condition in every case. In an attempt
307 to extract more meaningful information from the heterogenous PD-NOS diagnosis, these
308 analyses were performed a second time using the reclassified PD-NOS diagnoses detailed
309 above. The treatment effect in categorical response was significant only for PD patients
310 classified into Cluster B ($N = 16$ $CMH \chi^2(1) = 4.01$, $p < .05$, $OR = 15.33$, 95% CI: 0.84--
311 280.59) indicating that patients diagnosed with PD NOS whose concentration of
312 pathological personality traits was greatest in Cluster B had over 15 times greater odds of
313 responding to ADM, relative to CT. The treatment effect was not significant for either
314 Cluster A or Cluster C, although with a sample size of 8 in Cluster A, this test was
315 associated with extremely limited power (2/4 responded to CT, versus 1/4 in ADM). In

316 Cluster C, 32/47 (68%) responded to ADM, versus 10/19 (53%) in CT (CMH $\chi^2(1) =$
317 1.43, $p = .23$ OR = 1.93, 95% CI: 0.65--5.74). The treatment effect approached
318 significance for only one individual personality disorder re-classification, Borderline PD
319 ($N = 7$ CMH $\chi^2(1) = 2.88$, $p = .09$). Three out of four patients diagnosed with PD NOS
320 with predominantly borderline traits responded in the ADM condition, whereas 0 of 3
321 patients responded in the CT condition.

322 *Potential Confounds*

323 It is possible that the patients with and without PDs in this study differed on one
324 or more potentially confounding variables that could account for the observed effects. To
325 address this concern, 8 history of illness variables, 2 depression subtype variables, 4
326 composite axis-I comorbidity variables, and 7 demographic variables were examined to
327 determine whether the PD and Non-PD patients differed on any of them at the $p < .10$
328 level. As can be seen in Table 2, nine of these variables differed between the two groups.
329 To determine whether these variables might be driving the aforementioned effects, all 9
330 variables were simultaneously entered into each of the statistical models outlined above.
331 For the model predicting categorical response, the PD-status-by-treatment interaction
332 remained significant even with the simultaneous addition of all 9 variables ($\chi^2(1) = 5.59$,
333 $p = .02$). In the LOCF analysis, the interaction of interest dropped to the level of a non-
334 significant trend with the addition of the 9 covariates to the model ($F(1, 164) = 3.54$, $p =$
335 $.06$).

336 *Sustained Response at the Conclusion of the 12-Month Continuation Phase*

337 For the 12-month continuation phase, the survival rates of the 3 treatment
338 conditions (prior CT, cP-P, and cADM) were estimated for the PD and Non-PD groups.

339 Sustained response estimates for each group were calculated by computing the product of
340 these survival estimates and the group's treatment response rate (e.g., for patients in the
341 PD group who had received ADM treatment, survival estimates for both the cADM and
342 cP-P were multiplied by the percent of PD patients who responded to acute ADM
343 treatment). Analysis of these estimates revealed a significant treatment-by-PD-status
344 interaction in the percent of patients who showed a sustained response at the end of the
345 12 months ($\chi^2(2) = 6.13, p = .047$). The main effect of treatment was also significant (χ^2
346 $(2) = 11.83, p = .003$); however, the main effect of PD-status was not ($\chi^2(1) = 0.57, p =$
347 $.45$). For patients in the PD group, a significant main effect of treatment emerged ($\chi^2(2)$
348 $= 11.94, p = .003$). The wider bars in the figure show that despite the fact that a higher
349 proportion of these patients responded to treatment (and hence entered the continuation
350 phase) in the ADM compared to the CT conditions, an estimated $38 \pm 18\%$ of the total
351 sample of patients initially randomized to CT responded to treatment and remained well
352 throughout the continuation period. Although the relapse rate was higher for patients in
353 the cADM condition, nearly the identical estimated proportion of patients, $38 \pm 17\%$,
354 responded to treatment and remained well through the end of the continuation period.
355 Finally, patients who had previously received ADM but were withdrawn onto pill-
356 placebo tended to relapse at an extremely high rate. Only $6 \pm 9\%$ of patients randomized to
357 this condition exhibited sustained response. Specific contrasts revealed that prior CT and
358 cADM were each superior to cP-P on the sustained response variable ($\chi^2(1) = 9.80, p =$
359 $.002$ for cADM versus cP-P, and $\chi^2(1) = 9.15, p = .003$ for prior CT versus cP-P).

360 For patients in the Non-PD group, the main effect of treatment was not significant
361 ($\chi^2(2) = 4.54, p = .103$). The figure shows that for patients initially randomized to receive

362 CT, 43±17% exhibited sustained response. For patients initially randomized to receive
363 ADM treatment, an estimated 23±15% in the cP-P and 21±14% in the cADM conditions
364 remained well throughout this phase.

365 Discussion

366 The primary purpose of this investigation was to determine the effects of personality
367 pathology on two generally effective treatments for depression. In this sample of moderate-to-
368 severely depressed patients, short-term cognitive monotherapy proved relatively ill-suited for
369 patients with comorbid personality disorders. Indeed, CT did not outperform placebo after 8
370 weeks, and fewer than half of personality disordered patients had responded to CT by the end of
371 the 16-week treatment period. Those who did respond, however, tended to sustain their response
372 throughout the ensuing 12-month continuation phase.

373 Paroxetine, on the other hand, worked particularly well during the first 8 weeks to reduce
374 depressive symptoms for patients diagnosed with comorbid personality disorders, and it
375 maintained its advantage over CT in this subgroup through the remainder of the 16 week trial.
376 Although the personality-disordered and non-personality disordered groups differed in several
377 respects, including the incidence of comorbid anxiety disorders, none of these factors accounted
378 statistically for the differential treatments effects. Results from the continuation phase of the
379 study further support the conclusion that the medications had potent effects in this group in that
380 nearly all of the personality-disordered patients relapsed when withdrawn from medications,
381 whereas over half of those who remained on medications sustained their response throughout this
382 period.

383 The advantage of paroxetine among the personality-disordered patients was especially
384 evident among patients whose Axis-II symptoms were concentrated in the B Cluster, and other

385 researchers have reported findings consistent with these results.²⁷⁻²⁹ Russell et al., for example,
386 found higher rates of remission following treatment with the SSRI sertraline for patients
387 diagnosed with comorbid Cluster B disorders, compared to patients who did not have a PD
388 diagnosis.²⁸ Furthermore, Ekselius and von Knorring found a significant reduction in the
389 frequency of personality disorder diagnoses, including Borderline PD, in depressed patients
390 following treatment with sertraline. Crucially, this effect was not explained by reduction in the
391 severity of depressive symptoms.³⁰

392 An explanation of the beneficial effects of SSRIs for patients with Cluster B pathology is
393 suggested by converging findings from treatment and imaging studies in humans and from
394 behavioral studies in animals. Johnson et al. concluded in their review of the electrophysiology
395 and neuroimaging literatures that patients with Cluster B personality disorders, particularly
396 borderline personality disorder, display deficits in prefrontal cortical activity, especially in the
397 orbital prefrontal region.³¹ This area is thought to underlie the regulation of emotion and the
398 inhibition of impulsive aggression.^{31, 32} One hypothesis that is gaining support is that these
399 abilities are enhanced by SSRI-induced increases in serotonergic activity in critical frontal
400 regions. In studies of pigeons, the SSRIs fluoxetine, citalopram, and paroxetine have each been
401 shown to reduce impulsive behavior, operationalized using a delay of gratification paradigm.³³
402 Studies with patients diagnosed with Cluster B PDs have found that citalopram leads to a
403 substantial reduction in self-reported impulsive aggression.³² Similarly, the SSRIs fluvoxamine
404 and fluoxetine have, respectively, been shown to reduce mood lability and anger in patients with
405 Borderline PD.³⁴⁻³⁷ Consistent with the hypothesis, in one of these studies changes were
406 observed not only on a self-report measure of impulsive aggression, but also on an index of
407 prefrontal cortical metabolic activity.³⁷

408 These links among the pharmacological effects of SSRIs, changes in the functioning of
409 emotion regulation systems in the brain, and changes in maladaptive behavior suggest a
410 mechanism for the beneficial effects of SSRIs on the depressive symptoms experienced by
411 patients with comorbid personality disorders. The present findings, involving only clinical data,
412 motivate more direct tests of this hypothesis. Future studies should attempt to test whether
413 changes in prefrontal cortical functioning following SSRI treatment lead to changes in emotion
414 regulation and impulsive behavior, which, in turn, engender reductions in depressive symptoms.

415 The present findings further revealed that for depressed patients without personality
416 pathology, both cognitive therapy and antidepressant medication were more effective than
417 placebo during the first 8 weeks of treatment; however, a difference emerged between these two
418 treatments by the end of the 16 week trial. Specifically, patients without personality disorders
419 derived more benefit from cognitive therapy than from paroxetine. Cognitive therapy was
420 developed specifically to address the emotional and behavioral phenomena of depression. It may
421 be that cognitive therapy and other psychotherapies, such as behavioral activation therapy, that
422 focus on the pathologies of behavior in depression, are especially well suited to help depressed
423 patients overcome response initiation deficits that lead to passivity and disengagement from the
424 world. It may also be that patients with non-pathological personality functioning present fewer
425 obstacles in a treatment modality such as CT that requires engagement with the process of
426 therapy, and with the therapist's suggestions for change.

427 *Limitations*

428 The pattern of findings in regard to acute treatment response was consistent across
429 the three different statistical methods, and the test of significance for the interaction of
430 interest was met in two of the three. However, in the analysis that employed hierarchical

431 linear modeling (HLM), the test for an interaction of Treatment X PD Status X Time was
432 not significant. In the HLM procedure, unlike in the other two approaches, patients who
433 drop out are assumed to have continued to change, in a linear fashion and in the same
434 direction (improved vs. deteriorated) that they had changed prior to dropout. Thus, to the
435 extent that dropout rates differed across the treatments, estimates of improvement rates
436 will tend to be inflated in the condition(s) in which the highest dropout rates were
437 observed. Consistent with the observation that PD patients assigned to CT and Non-PD
438 patients assigned to ADM fared more poorly than the other two groups, these groups also
439 tended to drop out at higher rates, which is another indication that ADM is better-suited
440 to PD patients, and CT is better suited to patients without PD. Thus, although the
441 confound introduced by dropout can never be fully resolved statistically, in the present
442 sample both poorer response and higher rates of dropout tended to occur in the same
443 groups, lending support to the conclusion that ADM was the superior acute treatment for
444 PD patients, whereas CT was better for the Non-PD patients.

445 A second limitation involves the duration of the active treatments. The study from
446 which these data originate was designed to be an investigation of short-term treatments
447 for depression, and the differences that emerged herein between CT and ADM as a result
448 of PD status may have been due, in part, to the short-term nature of this design. That is,
449 given more time, CT might have been as effective as medications for patients with PDs
450 and ADM might have been as effective as CT for patients without PDs. Nevertheless,
451 short-term treatment was sufficient to reduce the symptoms of depression for a majority
452 of patients in both the PD and the non-PD subgroups, provided they received the
453 treatment that was more effective for their subgroup.

454 *Conclusions*

455 The pattern of results from this study suggests possible prescriptive
456 recommendations regarding short-term treatment for patients with moderate to severe
457 depression as a function of personality disorder diagnosis. The evidence from this study,
458 consistent with findings from other investigations, suggests that if patients have a
459 comorbid PD, paroxetine treatment is more likely than CT to alleviate symptoms in the
460 short term. Due to a higher relapse rate in ADM during the following 12 months,
461 however, the two treatments may produce roughly equivalent proportions of patients who
462 both respond to treatment and sustain that response, provided that medication is
463 continued and booster sessions are given to CT patients. Given the relatively low relapse
464 rate among PD patients who responded to CT, the combination of ADM and CT might be
465 especially valuable for these patients. Patients without a PD diagnosis fared better during
466 acute treatment and exhibited a higher sustained response rate in CT, compared to ADM.
467 Furthermore, these patients appeared to be equally susceptible to relapse following acute
468 treatment regardless of whether they were continued on medication or withdrawn onto
469 placebo. This pattern, if replicated, suggests that patients who do not have a comorbid PD
470 are more likely to respond to CT than to paroxetine, and they are more likely to sustain
471 this response with booster sessions of CT than with continued treatment with
472 medications.

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606 Figure caption

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608 Figure: The narrow bars display the proportion of patients who met response criteria in
609 the two treatments (ADM and CT) at the end of 16-week acute phase. The wide
610 bars represent the estimated proportion of patients who survived the 12-month
611 follow-up period without a relapse. Bars on the left half of the figure represent
612 patients diagnosed with comorbid personality disorders; bars on the right
613 represent patients who did not have a comorbid Axis-II diagnosis.

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Table 1: The distribution of personality disorder diagnoses in the sample

Personality Disorder	Total (N = 240)		ADM (N = 120)		CT (N = 60)		Placebo (N = 60)		X ²	p
	N	%	N	%	N	%	N	%		
Any Axis-II	116	48.3%	59	49.2%	27	45.0%	30	50.0%	0.37	0.83
Cluster C	74	30.8%	37	30.8%	17	28.3%	20	33.3%	0.35	0.84
Avoidant	45	18.8%	24	20.0%	9	15.0%	12	20.0%	0.74	0.69
Dependent	7	2.9%	3	2.5%	2	3.3%	2	3.3%	0.15	0.93
Obsessive-Compulsive	38	15.8%	17	14.2%	10	16.7%	11	18.3%	0.56	0.75
Cluster A	8	3.3%	3	2.5%	3	5.0%	2	3.3%	0.78	0.68
Paranoid	8	3.3%	3	2.5%	3	5.0%	2	3.3%	0.78	0.68
Schizoid	0	0.0%	0	0.0%	0	0.0%	0	0.0%	.	.
Cluster B	8	3.3%	4	3.3%	1	1.7%	3	5.0%	1.03	0.60
Histrionic	2	0.8%	1	0.8%	0	0.0%	1	1.7%	1.01	0.60
Narcissistic	7	2.9%	3	2.5%	1	1.7%	3	5.0%	1.32	0.52
NOS	35	14.6%	16	13.3%	9	15.0%	10	16.7%	0.37	0.83
Distribution after reclassification of PD NOS										
Cluster C	66	36.7%	47	39.2%	19	31.7%	.	.	0.97	0.33
Avoidant	39	21.7%	30	25.0%	9	15.0%	.	.	2.35	0.12
Dependent	8	4.4%	4	3.3%	4	6.7%	.	.	1.05	0.31
Obsessive-Compulsive	35	19.4%	23	19.2%	12	20.0%	.	.	0.02	0.89
Cluster A	8	4.4%	4	3.3%	4	6.7%	.	.	1.05	0.31
Paranoid	8	4.4%	4	3.3%	4	6.7%	.	.	1.05	0.31
Schizoid	0	0.0%	0	0.0%	0	0.0%
Schizotypal	0	0.0%	0	0.0%	0	0.0%
Cluster B	16	8.9%	9	7.5%	7	11.7%	.	.	0.86	0.35
Histrionic	2	1.1%	2	1.7%	0	0.0%	.	.	1.01	0.31
Narcissistic	7	3.9%	5	4.2%	2	3.3%	.	.	0.07	0.79
Borderline	7	3.9%	4	3.3%	3	5.0%	.	.	0.3	0.59
Antisocial	3	1.7%	1	0.8%	2	3.3%	.	.	1.53	0.22

The top portion of the table represents the raw distribution of personality disorder diagnoses in the sample. The lower portion represents the distribution after patients diagnosed with PD NOS were reclassified into the diagnostic category for which they had the highest concentration of symptoms.

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Table 2: Differences between the PD and Non-PD groups on potentially confounding variables

Potential Confound	Non-PD		PD		t / X²
	Mean / %	SD	Mean / %	SD	
History of illness					
Onset Age	25.0	12.8	19.2	10.8	3.3 *
Number of Previous Treatments	1.2	1.6	1.9	1.8	-2.9 *
Number of Previous Hospitalizations	0.1	0.3	0.3	0.8	-2.5 †
Duration of Illness (months)	34.1	45.1	59.0	88.6	-2.4 †
Dysthymia	19.2%		34.9%		5.7 †
Number of Prior Episodes	2.1	2.7	2.9	2.8	-2.0 ‡
Chronic MDD	45.7%		57.0%		ns
Recurrent MDD	69.2%		76.7%		ns
Depression Subtype					
Met DSM-IV specifiers for atypical features	17.0%		30.2%		4.9 †
Met DSM-IV specifiers for melancholia	26.6%		36.1%		ns
Axis-I Comorbidities					
Any anxiety disorder	44.7%		59.3%		3.8 †
Any other Axis-I disorder	1.1%		8.1%		Fisher's Exact Test †
Any substance use disorder	28.7%		31.4%		ns
Any eating disorder	17.0%		16.3%		ns
Demographics					
Married	38.3%		29.1%		ns
Female	62.8%		53.5%		ns
Employed	81.9%		84.9%		ns
Caucasian	80.9%		84.9%		ns
Age	40.1	12.3	39.7	10.7	ns
Education (years)	14.5	2.5	14.7	2.3	ns
Income (in thousands USD)	32.1	31.4	35.2	35.7	ns
Medication (Completers only)					
Dosage (mg)	34.4	8.8	34.1	8.6	ns
Augmentation	52.1%		42.3%		ns

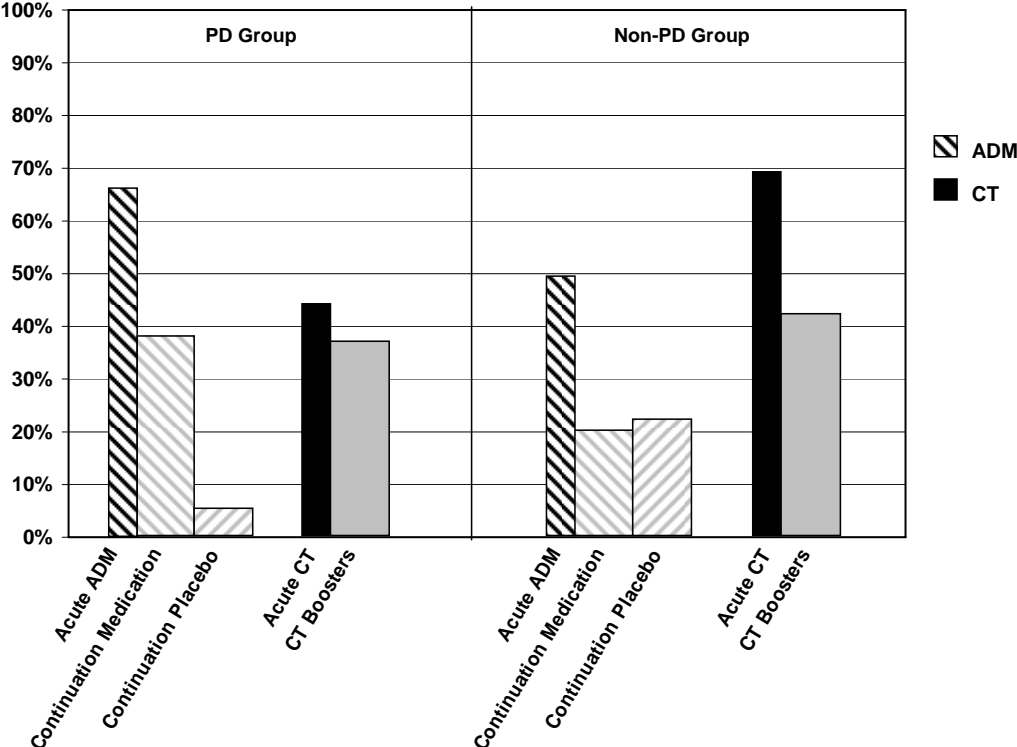
* p < .01

† p < .05

‡ p < .10

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622 **Figure:**
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