Do Comorbid Personality Disorders Moderate Panic-Focused Psychotherapy? An Exploratory Examination of the American Psychiatric Association Practice Guideline

Barbara L. Milrod, M.D.; Andrew C. Leon, Ph.D.; Jacques P. Barber, Ph.D.; John C. Markowitz, M.D.; and Elizabeth Graf, M.A.

Objective: The American Psychiatric Association (APA) practice guideline for panic disorder recommends psychodynamic psychotherapy for panic disorder patients with comorbid personality disorders. No data underlie this recommendation. This exploratory study assessed the moderating effect of personality disorder on psychodynamic and non-psychodynamic psychotherapy outcome.

Method: Forty-nine subjects with primary DSM-IV panic disorder were randomly assigned to 12 weeks of twice-weekly Panic-Focused Psychodynamic Psychotherapy or Applied Relaxation Training. The primary outcome measure was the Panic Disorder Severity Scale; the moderating effect of Axis II psychopathology on the Sheehan Disability Scale was also tested. The trial was conducted between February 2000 and January 2005.

Results: Twenty-four subjects (49%) met DSM-IV criteria for a Structured Clinical Interview for DSM-IV Axis II Disorders–diagnosed personality disorder, of whom 19 (79%) had a cluster C diagnosis. Presence of a cluster C diagnosis moderated treatment outcome. Such subjects experienced greater improvements in Panic-Focused Psychodynamic Psychotherapy than subjects without cluster C comorbidity.

Conclusions: Despite its small sample size, this exploratory analysis provides initial preliminary evidence corroborating the APA practice guideline recommendation. Future panic disorder clinical trials should explore Axis II moderator effects.

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Received July 26, 2006; accepted Oct. 20, 2006. *From the Department of Psychiatry, Weill Medical College of Cornell University (Drs. Milrod and Leon and Ms. Graf) and the New York State Psychiatric Institute (Dr. Markowitz), New York; and the Department of Psychiatry, University of Pennsylvania, Philadelphia (Dr. Barber).*

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Corresponding author and reprints: Barbara L. Milrod, M.D., Department of Psychiatry, Weill Medical College of Cornell University, 525 East 68th St., New York, NY 10021 (e-mail: bmilrod@med.cornell.edu).

The intersection of the DSM Axes I and II poses a clinical challenge. When clinicians discover personality disorders comorbid with Axis I diagnoses, should they alter their treatment approach? Are particular therapies more or less likely to benefit patients with multiaxial comorbidity? Unfortunately, this area has received relatively little attention, especially in anxiety disorder patients. The Axis II comorbidity of panic disorder is an interesting example, as many patients with panic disorder also have Axis II diagnoses, particularly in the ("anxious") cluster C.

In a descriptive study, Ozkan and Altindag[1] found panic disorder patients with comorbid personality disorders had greater clinical severity across anxiety, mood, and psychosocial domains than panic disorder patients without personality disorders. Few studies have examined the effect of Axis II on panic disorder treatment outcome. In the naturalistic, multisite Harvard-Brown study (N = 514), Massion et al.[2] found no negative impact associated with comorbid personality disorders, diagnosed by International Personality Disorder Examination,[3] on time to panic disorder remission. Another report found cluster C disorders were associated with longer duration of panic disorder,[4] potentially conflating apparent moderator effects of cluster C disorders with panic disorder duration, an identified indicator of poor prognosis.[5]

Studies of Cognitive Behavioral Therapy (CBT) for panic disorder have reported mixed effects of Axis II

comorbidity. Dreessen et al.[6] found no reduction in treatment effects in 2 open CBT trials of standard, time-limited CBT (31 and 57 patients with panic disorder and comorbid personality disorders). In contrast, Hoffart[7] reported worse CBT outcome for panic disorder inpatients with comorbid avoidant and dramatic traits (N = 57 with panic disorder and agoraphobia).

No empirical studies of psychodynamic psychotherapy as a sole treatment modality for panic disorder had been conducted before our group began its research.[8,9] Nonetheless, the American Psychiatric Association (APA) practice guideline for panic disorder[10] recommended psychodynamic psychotherapy for patients who have panic disorder and Axis II comorbidity, in part because psychodynamic psychotherapy and psychoanalysis have been widely used as treatments for character disorder. The guideline also noted that some data implied CBT might be less effective for patients with comorbid panic disorder and personality disorders, hence it described psychoanalytic psychotherapy as a reasonable clinical recommendation.[10] This recommendation lacked empirical support, since no randomized, controlled clinical trials (RCTs) of psychodynamic psychotherapy for panic disorder had been conducted.

Our recent trial provides preliminary data to examine the guideline's recommendation. This study compared Panic-Focused Psychodynamic Psychotherapy (PFPP)[11] and Applied Relaxation Training (ART) and found PFPP superior.[12] The current report explores whether a personality-disordered subgroup of patients with panic disorder particularly benefits from psychodynamic psychotherapy. Echoing the guideline, we hypothesized that PFPP would have greater efficacy than ART for panic disorder patients with Axis II comorbidity. We hypothesized that PFPP would specifically benefit panic patients with prominent underlying mixed feelings about self-assertion and autonomy[11] (viz., features that characterize cluster C disorders), as these conflicts commonly emerge in PFPP.

Study Design

After much consideration during the design phase, ART was chosen as the most appropriate comparison therapy for this first RCT of PFPP. Although the psychotherapy with the most robust evidence of demonstrated efficacy is CBT,[13] there were disadvantages to comparing PFPP to CBT at this stage. The standard approach to efficacy testing of new or untested treatments, pharmacologic or psychological, is an initial randomized comparison against a less active treatment, rather than against a standard reference treatment.[14] Relaxation therapies had been the most common comparison psychotherapies in the initial clinical trials of CBT for panic disorder.[15]

METHOD

An RCT comparing PFPP and ART treated 49 subjects with primary DSM-IV panic disorder, diagnosed on the Anxiety Disorders Interview Schedule for DSM-IV, Lifetime Version (ADIS-IV-L).[16] The ADIS-IV-L was selected because of its detailed focus on anxiety phenomena. ART was chosen as a comparison psychotherapy for this first efficacy trial of PFPP because of its high credibility and expectancy in patients with panic disorder,[17] while it has also been found to have less potency than CBT.[15,18] All subjects signed informed, written consent; the Weill Medical College Institutional Review Board approved the protocol. The trial was conducted between February 2000 and January 2005. Axis II comorbidity was diagnosed at baseline using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)[19] (the SCID-II has been shown elsewhere to have relatively good psychometrics; intraclass correlation coefficient [ICC] range, 0.65–0.98). Subjects were randomly assigned to PFPP or ART for 24 twice-weekly sessions over 12 weeks (for details, see Milrod et al.[12]). The primary dependent variable was the Panic Disorder Severity Scale (PDSS[20]; ICC = 0.87), a standard measure in most panic disorder outcome studies, chosen because it is a diagnosis-based, composite, global rating of panic severity, and the only specific measure of its kind. Independent, trained evaluators blinded to patient treatment group and therapist orientation performed all outcome assessments. The moderating effect of Axis II pathology on the Sheehan Disability Scale (SDS),[21] a self-rated scale that measures psychosocial function, was also tested.

Training of Independent Evaluators

Independent evaluators were trained to criterion on the ADIS-IV-L by Michael Schwalberg, Ph.D., evaluating patients presenting to the open trial of PFPP.[8,9] Independent evaluators were master's-level diagnosticians with ≥ 35 hours of training on the ADIS-IV-L, and ≥ 12 hours of training on the PDSS. B.L.M. trained raters to criterion on the PDSS. ADIS training requires the new diagnostician to corate 6 ADIS protocols with the experienced rater and to match diagnostic categories and severities in these 6 ADIS protocols, 3 administered by the trainer, 3 by the new rater. ADIS-IV-L raters corated 2 patients every 6 months to minimize drift. The PDSS was corated for 8 patients over 5 years in order to monitor interrater reliability. Raters were blind to patient assignment and to therapist orientation.

Therapeutic Interventions

Panic-Focused Psychodynamic Psychotherapy. The intervention of interest was a 12-week, 24-session (twice weekly) manualized psychoanalytic psychotherapy that preserves a psychoanalytic, transference-based framework

while consistently attending to the physical symptoms of panic disorder and agoraphobia.[11] Focus on the unconscious emotional significance of panic is central to the treatment, which emphasizes identifying and interpreting underlying psychological meanings of physical symptoms. The emotional significance of panic triggers is explored and interpreted. PFPP consistently helps patients to understand their internal emotional states. It is likely that this therapy addresses cluster C traits, as conflicts about the experience of rage at attachment figures are carefully explored. Panic patients commonly avoid aggression, expressing anger through dependent and controlling anxious neediness.[11] These characteristics and their connection to panic and agoraphobic avoidance are openly discussed. PFPP's focus on conflicted aggression detoxifies it, leading to improved autonomous function, a lessened sense of dependence on ambivalently loved objects, and more comfort with assertion and autonomy. Therapists focus on how agoraphobia and dependence on phobic companions maintain a childlike stance. PFPP involves no exposure.

Applied Relaxation Training. This therapy was also a 12-week, 24-session intervention, delivered twice weekly. This study used an adaptation of the Anxiety Treatment Project Relaxation Treatment Manual (J. A. Cerny, Ph.D., et al.; available from the authors on request). Progressive muscle relaxation training involves focusing of attention on particular muscle groups, tensing the muscle group for 5 to 10 seconds, attending to the sensations of tension, relaxing the muscle group, attending to the difference between the sensations of tension and relaxation, and suggestions of deepening relaxation. The number of muscle groups is gradually reduced from 16 to 8 to 4. Discrimination training, generalization, relaxation by recall, and cue-controlled relaxation (pairing the relaxed state to the word "relax") follow.

Home practice is required twice daily. By week 6, subjects apply relaxation skills to anxiety-provoking situations (in vivo exposure) in graduated fashion. Trained to identify early stages of anxiety, subjects are instructed to use relaxation as an active coping strategy whenever they become aware of tension and to practice relaxation regularly throughout the day in various situations in order to maximize generalization.

ART uses no interoceptive exposure. It is not designed to address characterological underpinnings to panic disorder.

Therapists

PFPP therapists. All 8 PFPP therapists were post–psychiatric residency M.D.s or Ph.D. psychologists. All had completed at least 3 years' psychoanalytic training at a psychoanalytic training institute. Their mean experience was 21 years (range, 2–40 years; SD 8.6). All had specific training in PFPP, entailing a 12-hour course and a pilot supervised videotaped case, as well as at least 2 years' clinical experience with panic disorder using psychodynamic psychotherapy.

ART therapists. The 6 ART therapists were post–psychiatric residency M.D.s or Ph.D. psychologists with 16 mean years of experience (range, 5–35 years; SD 11.3) (Mann-Whitney $p = .66$ between therapist groups). Their specific training in ART entailed a 6-hour course, a pilot supervised videotaped case, and a minimum of 2 years' clinical experience working with panic patients with ART and CBT. All ART therapists had extensive CBT experience for panic disorder, and used some form of relaxation training in their routine practice; 2 ART therapists used ART routinely in practice.

Therapist adherence. Adherence to treatments was monitored by trained adherence raters in each condition, who rated 3 videotaped sessions per patient/therapist dyad. Both therapist groups were found adherent to their administered treatment: PFPP therapists achieved mean adherence ratings of 5.5 on the PFPP Therapist Adherence Scale (B.L.M.; F. N. Busch, M.D.; available from the authors on request), Likert scales scored from 1–6. Four raters determined reliability by applying the PFPP Adherence Scale to videotapes of PFPP sessions. Mean interrater ICC was 0.92 ($N = 50$). The cutoff for acceptable levels of adherence is a score of 4 or higher on at least 5 of the 7 items. The ART Adherence Scale (M. W. Otto, Ph.D.; M. H. Pollack, M.D.; available from the authors on request) contains 3 items per session, each scored on Likert scales rated from 1 to 7. ART therapists achieved average adherence ratings of 6.2 out of 7 (12 tapes for each therapist). The cutoff scores were 5 out of 7 on all items scored for that session.

Data Analytic Procedures

The hypothesized moderator is the presence or absence at baseline of either any Axis II comorbidity or a specific Axis II cluster diagnosis. The hypotheses were tested using the general strategy for exploratory moderator analyses in RCTs described by Kraemer et al.,[22] whose criteria for treatment moderators require that (1) the potential moderator precede treatment; (2) because of randomization, the potential moderator be uncorrelated with form of treatment; and (3) a moderator of treatment "must be shown to have an interactive effect with treatment on the outcome."[22(p879)] That is, the treatment effect must be shown to vary across levels of the moderator.

Furthermore, Kraemer et al. recommend that "p values are not and should not be used to define moderators and mediators of treatment because then moderator or mediator status would change with sample size."[22(p881)] Thus, our analyses focused on the magnitude of the effect, not on significance testing, and focused on the primary RCT endpoint measure, the PDSS.[20] These exploratory analyses examined differential effects of treatment by

comparing those with and without Axis II comorbidity on the magnitude of the between-group (PFPP vs. ART) effect size. That is, Cohen's d for PDSS change (baseline–posttreatment) was estimated separately for those with and without an Axis II diagnosis. We considered medium differences in between–treatment group effect sizes (Cohen's $d > 0.50$) noteworthy.

The intention-to-treat principle was employed in primary analyses, in accordance with the study protocol, by carrying forward the last observation (LOCF), which was the baseline assessment for study dropouts if they refused assessment at dropout time. Supplemental analyses examined the sensitivity of this strategy to attrition by only including RCT completers. (Alternative strategies for analysis of repeated assessments over the course of the trial using mixed-effects linear regression models, for example, were not possible because assessments were not administered between baseline and endpoint.)

RESULTS

Baseline Demographics

Subjects were a mean of 33 years old. Seventy-one percent were Caucasian, 27% African American, and 2% Asian; 18% were Hispanic. The ART group contained a greater proportion of men (47% vs. 15%; 2-tailed Fisher exact $p < .03$). There were no other significant demographic differences between the 2 treatment groups.

Axis II Pathology

Forty-nine percent (N = 24) of subjects met criteria for a comorbid Axis II disorder. Thirty-one percent (N = 15) had 1 Axis II disorder, and 18% (N = 9) met criteria for more than 1. Thirty-nine percent (N = 19; 79% of all subjects with personality disorders) had at least 1 cluster C diagnosis, and 16% (N = 8) had at least 1 cluster B diagnosis. Only 5 subjects had non–cluster C Axis II diagnoses in the absence of a cluster C diagnosis. Frequencies of individual personality disorders were as follows: obsessive-compulsive 20% (N = 10), avoidant 14% (N = 7), dependent 12% (N = 6), paranoid 12% (N = 6), and narcissistic 10% (N = 5). Cluster C disorders were not associated with longer panic disorder duration in this sample (Mann-Whitney $p = .23$). Presence of Axis II diagnosis did not differ significantly by treatment group (Fisher exact = 0.396), and cluster C disorders did not differ between groups either (Fisher exact = 0.596).

Evaluation of the Moderator Effect

We evaluated differential treatment effects of PFPP and ART, for subjects with and without Axis II pathology. Axis II was operationally defined Axis II in 3 different ways. Separate analyses compared subjects with versus without (1) any Axis II disorder, (2) cluster C disorders, or (3) cluster B disorders. Treatment outcome was assessed using the PDSS. We conducted no specific moderator analyses of cluster A because only 6 subjects carried a cluster A diagnosis, paranoid personality disorder, of whom 5 were randomly assigned to PFPP. This distribution is inconsistent with the Kraemer et al.[22] criterion requiring moderator effects to be uncorrelated with treatment group. (It is noteworthy, however, that the small number of subjects with comorbid paranoid personality disorder randomly assigned to PFPP did well [mean PDSS change = 9.4 (SD = 5.7)]: few studies support the utility of psychodynamic interventions for this disorder.)

Clinically meaningful, moderate-sized treatment effects appeared between treatment groups in patients without Axis II pathology, but still more substantial treatment effects arose in subjects who had Axis II comorbidity (Table 1). PFPP appeared still more advantageous than ART for subjects with an Axis II disorder (Cohen's $d = 1.19$) relative to those without an Axis II disorder (Cohen's $d = 0.55$). Cluster C disorder also appeared to moderate the treatment effect (cluster C: $d = 1.35$; no cluster C: $d = 0.69$). No moderating effect of cluster B was apparent (Cohen's $d = 1.10$ with cluster B vs. 0.91 without cluster B).

We also examined the moderating effect of Axis II comorbidity on changes in psychosocial functioning, as measured on the SDS. Overall outcome differences between treatment groups were more pronounced in the domain of panic symptom improvement than in psychosocial functioning (Cohen's $d = 0.95$ between groups on PDSS, while $d = 0.74$ on SDS, both favoring PFPP).[12] The pattern of the moderator effects of Axis II and cluster C pathology on treatment effects for improvement in psychosocial function was inconsistent (Tables 1 and 2). For instance, in the analyses that involved LOCF imputation (Table 1), the PFPP effect was greater for those with a comorbid Axis II disorder (Cohen's $d = 0.83$ vs. 0.59), but smaller for those with a cluster C disorder ($d = 0.64$ vs. $d = 0.74$).

Sensitivity analyses compared the results from the above LOCF-imputed and the completer data sets. Ten subjects dropped out, of whom 3 provided assessments at dropout. This resulted in incomplete data from 1 PFPP and 6 ART subjects who refused termination assessment (Table 2). The apparent moderator effect persisted when we limited analyses to subjects who completed termination ratings. In the completer analyses, between-group effect sizes for the PDSS were as follows: Axis II ($d = 1.01$ for patients with any Axis II diagnosis vs. 0.47 for those without one), cluster C ($d = 1.13$ vs. 0.51), cluster B ($d = 0.80$ vs. 0.66), all favoring PFPP.

DISCUSSION

Few randomized controlled studies have examined the efficacy of psychodynamic treatments for anxiety

Table 1. Moderator Effects of Any Axis II Disorder and Cluster B and C Disorders on Panic-Focused Psychodynamic Psychotherapy (PFPP) and Applied Relaxation Therapy (ART) for Panic Disorder: LOCF Used for Dropouts

Personality Disorder	N	PDSS Change Pre–Post, Mean (SD)	Between-Group Effect Size	N[a]	SDS Change Pre–Post, Mean (SD)	Between-Group Effect Size
Any Axis II disorder?						
No						
PFPP	15	7.3 (5.4)	0.55	15	5.9 (6.5)	0.59
ART	10	4.0 (6.4)		10	2.2 (5.2)	
Yes						
PFPP	11	9.3 (4.7)	1.19	11	9.3 (8.1)	0.83
ART	13	2.5 (4.5)		12	2.3 (7.3)	
Cluster B?						
No						
PFPP	23	7.9 (5.0)	0.91	23	6.8 (7.6)	0.72
ART	18	3.1 (5.5)		18	1.8 (5.1)	
Yes						
PFPP	3	10.0 (6.6)	1.10	3	11.3 (0.6)	0.78
ART	5	3.6 (5.1)		4	4.6 (11.0)	
Cluster C?						
No						
PFPP	16	7.3 (5.2)	0.69	16	6.7 (7.0)	0.74
ART	14	3.6 (5.5)		14	1.9 (4.7)	
Yes						
PFPP	10	9.4 (4.9)	1.35	10	8.4 (7.9)	0.64
ART	9	2.6 (5.2)		8	3.0 (8.7)	

[a]Ns differ due to missing data on the SDS.
Abbreviations: LOCF = last observation carried forward, PDSS = Panic Disorder Severity Scale, SDS = Sheehan Disability Scale.

disorders, much less the effect of comorbidity on their outcome. This, the sole randomized controlled trial of psychoanalytic psychotherapy as monotherapy for DSM-IV panic disorder, demonstrated efficacy of PFPP in comparison with ART.[12] The exploratory secondary analyses presented here are the first to address the APA practice guideline recommendation for panic disorder. Our preliminary results revealed greater superiority of psychodynamic treatment for subjects with cluster C comorbidity than for those without cluster C disorders, in the domain of panic disorder symptom resolution. As only 5 subjects with Axis II diagnoses lacked a cluster C disorder, the cluster C effect could not be disentangled from other Axis II effects in this sample. The between–treatment group effect size for those with Axis II comorbidity was substantially larger than that for those without Axis II pathology. These results provide initial evidence of personality pathology as a moderator of psychoanalytic psychotherapy on our primary outcome measure. Although comorbidity is typically an unwelcome, negative prognostic indicator, our results suggest the relative efficacy of PFPP was enhanced with Axis II comorbidity. In contrast, this moderating effect was not present for psychosocial functioning.

The results of this preliminary investigation are consistent with the APA practice guidelines. As the data from our small RCT support the hypothesis articulated in the guideline, the results must be considered as hypothesis-generating rather than hypothesis-confirming. In other words, our results should guide not clinical decision-making, but rather the design of future studies. Should these findings be confirmed in a subsequent study specifically designed to test the moderating effect of Axis II, they would have clinical importance, as patients with panic disorder commonly have Axis II, and predominantly cluster C, comorbidity.

Clinically, the differential treatment results are unsurprising, as PFPP addresses aspects of panic disorder patients' passivity and childlike dependence through exploration and articulation of transference fantasies, facilitating more adult behavior. By contrast, therapist-guided exposure protocols do not specifically address these functional or characterological issues. Such therapies can, if viewed through a psychoanalytic lens, potentially foster continued dependence on authority figures like the therapist, while overlooking underlying, enduring psychological conflicts that maintain the patient's sense of incompetence. The psychodynamic approach to these characterological phenomena aims to empower such patients to become more active and assertive by helping patients to articulate the fantasies that underlie their inhibitions regarding being more autonomous, perhaps enhancing symptomatic outcome.

These results clearly do not contradict the APA practice guideline recommendation, yet this study provides inadequate evidence to fully support it. As noted, a comprehensive test of our hypothesis requires an RCT designed to test the question of treating comorbid panic disorder and cluster C. The sample might be enriched by overrepresentation of subjects with cluster C disorders (perhaps as many as half the study sample) and

Table 2. Moderator Effects of Any Axis II Disorder and Cluster B and C Disorders on Panic-Focused Psychodynamic Psychotherapy (PFPP) and Applied Relaxation Therapy (ART) for Panic Disorder: Dropouts Without Termination Data Were Eliminated From Analyses

Personality Disorder	N	PDSS Change Pre–Post, Mean (SD)	Between-Group Effect Size	N[a]	SDS Change Pre–Post, Mean (SD)	Between-Group Effect Size
Any Axis II disorder?						
No						
PFPP	14	7.8 (5.2)	0.47	14	6.3 (6.6)	0.56
ART	8	5 (6.8)		8	2.8 (5.7)	
Yes						
PFPP[b]	11	9.3 (4.7)	1.01	10	10.2 (7.8)	0.76
ART	9	3.7 (5.1)		8	3.6 (8.9)	
Cluster B?						
No						
PFPP	22	8.2 (4.8)	0.66	21	7.5 (7.6)	0.71
ART	14	3.9 (6.0)		14	2.3 (5.7)	
Yes						
PFPP[b]	3	10 (6.6)	0.80	3	11.3 (0.6)	0.24
ART	3	6 (5.6)		2	9.3 (16.6)	
Cluster C?						
No						
PFPP	15	7.8 (5.0)	0.51	15	7.1 (7)	0.66
ART	10	5 (6.0)		10	2.7 (5.5)	
Yes						
PFPP[b]	10	9.4 (4.9)	1.13	9	9.3 (7.8)	0.60
ART	7	3.3 (5.8)		6	4 (10)	

[a]Ns differ due to missing data on SDS.
[b]LOCF and no LOCF results for Axis II PFPP conditions are identical because all data were available for all PFPP subjects who had comorbid Axis II pathology.
Abbreviations: LOCF = last observation carried forward, PDSS = Panic Disorder Severity Scale, SDS = Sheehan Disability Scale.

treatment cells stratified by presence or absence of cluster C pathology.

A limitation of this study is that our exploratory analyses did not compare 95% confidence intervals for the effect sizes, which in small samples tend to be wide.[23] The small sample size yields not only greater uncertainty about the estimates, but also very small numbers of subjects with individual personality disorders to assess their specific moderator effects.

Future research should repeat Axis II assessments at termination, since Axis II diagnoses have been known to fade either with Axis I treatment[24] or spontaneously.[25] Furthermore, this trial did not involve CBT, the most commonly recommended psychotherapy for panic disorder, which may or may not be equally efficacious for comorbid panic disorder and cluster C disorders. This leaves the relative utility of CBT and PFPP for patients with panic disorder and Axis II disorders uncertain.

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