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WHAT KIND OF PREDICTORS ARE WE TALKING ABOUT?

A COMMENTARY ON *CONFORMITY TO PROTOTYPICAL THERAPEUTIC PRINCIPLES AND ITS RELATION WITH CHANGE IN REFLECTIVE-FUNCTIONING IN THREE TREATMENTS FOR BORDERLINE PERSONALITY DISORDER* (KIVITY ET AL., 2019)

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Abstract

Objective: To clarify the state-of-the-art criteria for defining predictors, to propose how the term predictor and related ones should be interpreted in Kivity et al.'s research, to determine which study's conclusions should be ignored and which should be considered for clinical practice or research purposes, and to recommend future directions in the research of predictors in psychotherapy for borderline personality disorder. **Method:** To propose how the term predictor and related ones should be interpreted in Kivity et al.'s research, we shall follow the modern MacArthur approach for defining predictors. **Results:** It is impossible to determine if the variable "adherence to the TFP prototype at Timepoint 2" occurs before change in reflective-functioning and thus, it is impossible to determine if it should be interpreted as an intervening predictor or merely as an outcome; therefore, the study's conclusions regarding this variable as a predictor should be ignored for future research purposes. Although "lower pre-treatment reflective-functioning" fulfills the defining criteria of a moderator, owing to the lack of evidence of its clinical significance, it should be ignored for clinical practice. **Conclusions:** No strong inferences about predictors in TFP with clinical or research relevance can be drawn from the study.

***Keywords*:** Mediators; Moderators; Randomized Controlled Trials; Reflective-Functioning; Transference-Focused Psychotherapy

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The term predictor and related ones were used more than 60 times in Kivity et al.'s paper (Kivity et al., 2019), but what kind of predictors are they talking about? It seems to us that sometimes they are talking about moderators, sometimes about mediators, and sometimes neither of these—the ambiguity possibly arising from the use of the Baron & Kenny approach to predictors (Baron & Kenny, 1986; Kraemer, Kiernan, Essex, & Kupfer, 2008). This ambiguous use of the concepts pertaining to predictors—i.e., factors that influence outcome—is quite common in clinical research literature (Kraemer, 2014, 2016b; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001).

The issue is important because the inferences clinicians and researchers draw from randomized clinical trials (RCT) about clinically significant predictors, that is, moderators and mediators, are correspondingly ambiguous or wrong (Kraemer, 2016b). When these ambiguous or erroneous inferences reach clinical practice, they do not fit with what clinicians see—so that findings do not help determine which patients would benefit from the intervention and how to maximize the benefit of the intervention—; and when they serve as foundation for the design of new clinical research, they perpetuate the vicious cycle. In short, the proper use of the concepts of predictors in clinical research should guide clinicians and researchers regarding "which trials might best be ignored and which carefully considered" (Kraemer, 2016b).

The objective of this Commentary is to clarify the state-of-the-art criteria for defining predictors—based on the MacArthur approach—, to propose how the term predictor and related ones should be interpreted in Kivity et al.'s research in line with these criteria, to determine which study's conclusions should be ignored and which should be considered for clinical practice or research purposes and, to recommend future directions in the research of predictors in psychotherapy for borderline personality disorder. Because the primary focus of the research were hypotheses pertaining predictors in Transference-Focused Psychotherapy (TFP), the recommendation to "ignore nonsignificant findings in the research literature as inconclusive" (Kraemer, 2016b), and space limitations, we will focus only on the following statistically significant conclusions (with their associated hypotheses): (a) adherence to the TFP prototype at Timepoint 2 "predicts" change in reflective-functioning and (b) lower pre-treatment reflective-functioning is "correlated" with larger improvements in reflective-functioning during treatment. Nevertheless, the analysis that follows is applicable to any of the study's statistically significant conclusions.

State-Of-The-Art Criteria for Defining Predictors in RCT

A predictor (M) is an event different from treatment choice—measured with a certain instrument—that is statistically associated with the outcome (O) in a RCT. There are two kinds of predictors: baseline predictors (B) and intervening predictors (I). Baseline predictors correspond to those events that occur *before* the

choice between two or more possible treatments is made—in the case of RCTs, before randomization. Intervening predictors are events that occur *after* treatment choice has been made (T) and *before* the outcome occurs (Kraemer, 2016b). (For a clear depiction of these concepts please refer to Kraemer [2016b]). In short, what determines if an event (namely, a variable) is a baseline or intervening predictor is its temporal relationship with treatment choice (T) and outcome (O).

There are two kinds of baseline predictors: moderators and nonspecific predictors of outcome (Kraemer, 2016b). A baseline predictor is a moderator if and only if there is no statistical association between T and B, and the effect size of T on O varies depending on the value of B (Kraemer, 2016b; Kraemer et al., 2008; Kraemer, Wilson, Fairburn, & Agras, 2002). A baseline predictor is a nonspecific predictor of outcome if and only if there is no statistical association between T and B, and the effect size of T on O does not vary depending on the value of B (Kraemer, 2016b). Of these two baseline predictors, only moderators have clinical and research implications because they tell us for whom or under what conditions the treatment works (Kraemer, 2016b; Kraemer et al., 2008; Kraemer et al., 2002). Therefore, nonspecific predictors of outcome should be ignored and moderators considered to determine which of the different available treatments will yield the largest outcome effect size for a particular patient.

There are four kinds of intervening predictors: mediators, influences on the outcome independent of treatment choice, consequences of treatment independent of the effect of T on O, and predictors of outcome moderated by the effect of treatment choice. An intervening predictor is an influence on the outcome independent of treatment choice if and only if there is not a statistical association between T and I, I has a statistical association with the effect size of O, and the effect size of I on O does not vary depending on the value of T. An intervening predictor is a predictor of outcome moderated by the effect of treatment choice if and only if there is not a statistical association between T and I, I has a statistical association with the effect size of O, and the effect size of I on O varies depending on the value of T. An intervening predictor is a consequence of treatment independent of the effect of T on O if and only if there is a statistical association between T and I, and I does not account for any of the effect size of T on O (Kraemer, 2016b). An intervening predictor is a mediator of T on O if and only if there is a statistical association between T and I, and I accounts for part or all the effect size of T on O (Kazdin, 2007, 2009; Kraemer, 2016b). Of these four intervening predictors only mediators have clinical and research implications because they tell us how or why the treatment works and how treatment outcome could be enhanced (Kraemer, 2016b; Kraemer et al., 2002). Therefore, influences on the outcome independent of treatment choice and predictors of outcome moderated by the effect of treatment choice should be ignored to determine which of the different available treatments will yield the largest outcome effect size for a

particular patient; consequences of treatment independent of the effect of T on O should be ignored and mediators considered to perform additional randomized controlled trials designed to manipulate the intervening predictors by optimizing the treatment and enhance the outcome effect size attributable to these variables.

How the Term Predictor and Related Ones Should be Interpreted in Kivity et al.'s Research

To propose how the term predictor and related ones should be interpreted in Kivity et al.'s research, we shall follow the principles of fairness—that is, interpreting the research as close as possible to the author's intentions—and charity—that is, if uncertainty exists, interpreting the research to render it stronger rather than weaker (Harrell, 2016).

The experimental design characteristics and findings we shall use as premises for the interpretation are (a) adherence to the TFP prototype at Timepoint 2 was measured at approximately three-months post-randomization—since authors considered 3 months were not late enough for disentangling adherence from outcome—; (b) reflective-functioning was measured at baseline and at the end of treatment (1-year post-randomization); and (c) lower pre-treatment reflective-functioning was correlated with larger improvements in reflective-functioning at post-treatment (r=-0.45) (Kivity, et al., 2019).

High Adherence to the TFP Prototype at Timepoint 2 "Predicted" Larger Improvements in Reflective-Functioning in the TFP Arm, but not in the DBT and SPT Arms

What kind of predictor are we talking about? Here the variables are *adherence to the TFP prototype at Timepoint 2* (predictor) and *change in reflective functioning* (outcome). Since *adherence to the TFP prototype* can only occur after T—i.e., after randomization—(premise a) it is clear that we could only talk about an intervening predictor (I) or an outcome (O) itself. Nevertheless, in order to I be an intervening predictor, I must occur before O, and this is impossible to determine with the actual experimental design of Kivity et al.'s study because reflective-functioning was measured only at pre- and post-treatment (premise b). The authors seem to account for this problem assuming that 3 months were not "late enough" for disentangling adherence from outcome, but this assumption might not hold (Murphy, Cooper, Hollon, & Fairburn, 2009) because TFP includes psychoeducation about borderline personality disorder as part of the initiation of therapy (Yeomans, Clarkin, & Kernberg, 2015) and the following reflection by the patient upon the diagnosis can stimulate the patient's interest in his or her internal mental states (Hersh, McCommon, & Golkin, 2019) and thus enhance reflective-

functioning before the 3 months point in therapy. This has precedent: at least some symptoms themselves—anxiety, depression, self-harm, rages and promiscuity, among others—are expected to reduce in the first few weeks or months in therapy (Gunderson & Links, 2014). Considering all of this, based on the study's experimental design it is impossible to determine if the variable *adherence to the TFP prototype at Timepoint 2* occurs *before* change in reflective-functioning and therefore, it is impossible to determine if it should be interpreted as an intervening predictor or merely as an outcome. Therefore, the study's conclusions regarding this variable as a predictor should be ignored as rationale to perform additional randomized controlled trials designed to manipulate *adherence to the TFP prototype at Timepoint 2* by optimizing the treatment and enhance the outcome effect size attributable to this variable.

Lower Pre-Treatment Reflective-Functioning is "Correlated" with Larger Improvements in Reflective-Functioning at the End of Treatment

Can we talk about a predictor? Yes. Although this analysis was performed to examine the possibility of "reverse causation" (Kivity, et al., 2019), it is interesting because lower pre-treatment reflective-functioning fulfills the aforementioned defining criteria of a moderator. Here the variables are *lower pre-treatment reflective-functioning* and *change in reflective-functioning at the end of treatment*. *Pre-treatment reflective-functioning* occurs before treatment choice—that is, before randomization, implying there is not a statistical association between T and M—and thus, we could talk about a baseline predictor. Since the effect size of T on O varies depending on the value of B (premise c), then *pre-treatment reflective-functioning* is a moderator. Is something missing? Yes. In order to be able to interpret the clinical significance of the finding, it would be necessary an appropriate effect size calculation—such as success rate difference (SRD)—and its associated confidence interval (Kraemer, 2016a, 2016b). Although promising, owing to the lack of evidence of its clinical significance, considering *lower pre-treatment reflective-functioning* as a moderator should be ignored to determine if TFP would yield the largest outcome effect size for a particular patient compared to the other different available treatments.

Conclusion and Future Directions

In conclusion, no strong inferences about predictors in TFP with clinical or research relevance can be drawn from Kivity et al.'s study.

To explore the hypothesis that *adherence to the TFP prototype* is a mediator of TFP on *change in reflective functioning*, a future RCT should measure the variables *adherence to the TFP prototype* and *change in reflective-functioning*

simultaneously and frequently from the beginning and throughout treatment (this might require an instrument to measure reflective-functioning that is easier to apply, such as the self-report Reflective Functioning Questionnaire [Luyten, Malcorps, Fonagy, & Ensink, 2019]); this new design would allow to determine if *adherence to the TFP prototype* occurs before *change in reflective-functioning* (Murphy et al., 2009). Then, if temporal precedence were established, SRD and its associated confidence interval should be calculated; this would allow to interpret the clinical significance of the finding (Kraemer, 2016b). Finally, if this results in a clinically significant difference between groups, an additional RCT addressing TFP in borderline personality disorder could be performed to validate *adherence to the TFP prototype* as a mediator based on a strong a priori hypothesis. In this additional RCT, the treatment should be optimized to manipulate *adherence to the TFP prototype* and enhance the effect size of *change in reflective-functioning* attributable to this mediator; the study must be sufficiently powered to detect the expected SRD (Kraemer, 2016a).

To explore the hypothesis that *lower pre-treatment reflective-functioning* is a clinically significant moderator of TFP, Kivity et al. could calculate, with the same data set, the SRD and its confidence interval. If this results in a clinically significant difference between groups, a future RCT addressing TFP in borderline personality disorder could be performed to validate *lower pre-treatment reflective-functioning* as a moderator based on a strong a priori hypothesis. In this additional RCT, the sample should be stratified into two strata based on the hypothesized moderator and the study must be sufficiently powered to detect the expected SRD (Kraemer, 2016a).

If *lower pre-treatment reflective-functioning* were proven to be a moderator and *adherence to the TFP prototype* a mediator, the contribution to clinical practice and policy-making would be outstanding.

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