Author's response to reviews

Title: Illicit drug use and antisocial personality traits at intake to treatment predicts cumulative retention

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Author's response to reviews: see over
Responses to reviewers’ comments

Dr. DiPaula

Minor essential Revisions:
1. Methods: (2nd to last sentence) ...and seen by a senior consultant psychiatrist who initiated and SUPERVISE (verb tense error)buprenorphine...
   • This has been changed

2. Subjects: (3rd sentence). The remaining subjects were 76% men. Not grammatically correct.
   • This has been changed to “97 men and 26 women”

3. Data presented in Subjects section would be more appropriate under results as opposed to methods.
   • Has been moved to the results section. An additional header has been added under this section

4. Results page 11 remove comma after As can be seen,... Also tense from this paragraph should probably be past not current based on previous paragraph.
   • This has been reworded

5. Discussion 1st sentence—may want to include reference.
   • We have added some references

6. Discussion 3rd paragraph, 1st sentence—may want to include reference.
   • We have added some references

Dr. Krampe

Throughout the paper, we have replaced the term relapse as a descriptor of the outcome with the term “cumulative retention”. We agree with Dr. Krampe that this is a much more precise description of the outcome.
Abstract, Methods: "At baseline, subjects were administered the Structured Clinical Interview for DSM-IV-II …" It should be made clear in the abstract that symptoms of a history of conduct disorder, as well as symptoms of avoidant personality disorder are based on self-report from the SCID-II screening questionnaire.

- We have changed this in the abstract

Abstract, Conclusion: "Patients who have … more severe symptoms or a history of conduct disorder before intake into treatment may be candidates …." This statement is misleading. Does it mean 'patients who have a greater extent of psychiatric distress, and / or a history of conduct disorder'? Or does it mean 'patients with more severe symptoms of a conduct disorder or a history of conduct disorder'? "history of conduct disorder before intake into treatment" sounds strange.

- We have reworded this section

- Background, page 3, paragraph 1: "It has long been well-known that a large proportion of patients with addiction relapse during or after treatment [1]. Identifying predictors of risk of relapse in different treatment models may provide valuable information about what type of patients can best be helped in what type of treatment" Please give also some recent references. Is relapse still a major problem in contemporary treatment programs? Is there evidence for any improvements during the last 40 years? Why can identifying predictors of relapse help to chose better treatment alternatives?

- We have added some more recent references

- We have reworded the statement to “Identifying predictors of risk of relapse in different treatment models may provide valuable information about what type of patients need extra services to obtain a satisfactory result in treatment”

Background, page 3, paragraph 1: "In an older meta-analysis of predictors of relapse to opiate use, it was found that …" Were the reported characteristics independent predictors of relapse? Did they differ with regard to predictive power?

- The meta-analysis did not mention independence, and did not mention multivariate results. Effect sizes were generally small, and several meta-analyses showed indication of significant heterogeneity. A statement to this effect has been added.
Background, page 4, paragraph 3: "The aim of this study was to study predictors of relapse in a consecutive cohort of buprenorphine treated patients. Based on the literature, we predicted that antisocial personality disorder, polysubstance involvement at baseline, and psychiatric symptoms at baseline, and lower levels on the Sense of Coherence scale would predict relapse." Concerning outcome this is a clear definition: Relapse. Actually it is also time to relapse that is investigated (see also comments to the title). Concerning predictors, the terms should be more specific, e.g.: Number of self-reported symptoms of a conduct disorder before age 15, number of positive test results for different illicit drugs in urine analysis at intake, severity of self-reported general psychiatric distress, and extent of subjective sense of coherence.

- We have changed the term used to describe the endpoint to “cumulative retention probability”. We have also specified the items used to measure the predictors as suggested.

Methods, page 4, paragraph 4, page 5, paragraph 1: Please give information about inclusion and exclusion criteria of the study, and if possible, about inclusion process: How many subjects were eligible? How many patients that were assessed for eligibility did not participate, is there any clinical information about patients who did not participate?

- We have now added the single inclusion criterion (beyond being admitted to the clinic), which was to complete the 4 weeks stabilization and detoxification period. It was at the end of this period that patients completed the SCID-Screen, and therefore subjects who did not complete this period did not have sufficient data for the analyses.

Methods, Assessments, page 7 and 8, SCID-II: Was there also an assessment of Axis-I disorders with SCID-I? If not, why so? The impact of personality disorder symptoms may be associated with the impact of Axis-I disorders. As can be concluded from the description of subjects on page 9, therapists did also make the SCID-II interview. This information should be given already in the description of assessment. Do SCID-II interview diagnoses of personality disorders also predict time-to-relapse in this study?

- We did not do the SCID-I for this study. We considered using the interview-based diagnoses, but unfortunately as this is a routine clinical setting, we did not have reliability data on the SCID-II interviews. As there is plenty of data to support the concurrent validity
of the SCID-II screen as a dimensional measure of personality pathology, we chose to use the SCID-Screen.

There is one major problem with the SCID-II screening instrument: Items concerning features that are not related to conduct disorder before age 15 are easily confused with items concerning current state of psychosocial functioning. The item formulations are simply taken from DSM criteria, and they do not clearly address stable personality features like the items of known personality inventories do. Only the instruction requests that participants rate their experience, feelings, attitudes and behaviors of both their previous and recent life. How did you make sure that patients really judged their personality and not only their current experience of the last months?

The reasons for why only the questionnaire data were used are not convincing: If the questionnaire scores and the interview scores are highly correlated than why not analyzing both data sets? If the interview data are too susceptible to interviewer bias, why are they supposed to be highly correlated to questionnaire data? Are the interview data really not usable when carried out by experienced clinicians? This would mean that thousands of studies based on SCID-II interviews are methodologically not sound. However, there are other reasons to prefer the questionnaire data:

There are good reasons that dimensional measurements of personality disorder traits are more valid than categorical measurements of personality disorders. Perhaps an argumentation that goes in the direction "dimensional versus categorical" is more convincing.

- Items from the SCID-Screen other than conduct disorder have now been omitted, based on the reviewer’s comment made elsewhere that the number of covariates is in excess.

- We have added a statement under the analyses section to the effect that a dimensional approach was selected for the analyses, along with some references

- We have added correlations for conduct disorder from the references given. For conduct disorder, the effect sizes were $r>0.7$ for both correlation with adult antisocial behaviour and temporal stability, so we have removed the word “moderately”

Methods, Statistical analysis, page 10: There are several issues: (1) Why is the defined primary outcome "relapse" changed to "involuntary discharge"? (2) It seems that the Cox proportional hazard model has 19 simultaneously included covariates. Please do either cite statistical literature that confirms that the sample size is big enough for 19 covariates, or choose a strategy that is based
on stepwise inclusion of predictors (as example see Krampe et al. Personality disorder and chronicity of addiction as independent outcome predictors in alcoholism treatment. Psychiatr Serv 2006;57:708-12). (3) The SCID-II screening questionnaire has different numbers of criteria for the different personality disorders. Thus the different "personality disorder subscales" differ with regard to the highest number of points patients can reach, e.g. avoidant personality: 7; narcissistic personality: 16. In order to make the criteria counts of the different personality disorder variables comparable or equivalent, the specific number that the patients reached for a given disorder should be divided by the maximal reachable number of this disorder. In other words, percentages of maximum numbers would be determined. This procedure is similar to the calculation of the subscale scores of the SCL-90-R. (4) Why are the SCL-90-R subscales depression and anxiety mentioned as predictors, what happened to the GSI? According to the description of SCL-90-R and Table 2, only the GSI is used. Why is GSI not mentioned as a predictor but shown in Table 2? This becomes very confusing (see also comments to Table 2).

- This has been corrected. We are sorry for the uploading of the wrong table 2. We will not follow the reviewers recommendation to standardize the predictors.

- Upon reading the reviewers comments, we decided to drop a large number of co-variates, leaving only three that we felt had the strongest basis in the literature, along with age and gender. The literature concerning power in survival analysis is quite complex and contradictory. We found it prudent to follow the advice to reduce the number of covariates. However, we did not chose to use a statistical stepwise regression. Stepwise models are becoming obsolete because they tend to capitalize heavily on chance.

- While the standardization of predictors may provide an illusion of comparability, it is in fact not necessarily meaningful to do so. Is age or conduct disorder more strongly associated with attrition? This is a conceptually meaningless comparison.

Results, page 11, paragraph 2: "The observation period ranged from one week to 64 months." Can you give the Kaplan–Meier estimate of cumulative abstinence probability at month 64 and mean survival time in days?

- Since the follow-up time varied, the retention probability at month 64 is not meaningful. We have however provided the median survival time.
Results, page 11, paragraph 3, Table 2: Results reported in the text and in Table 2 are inconsistent. This is extremely confusing. If I am not mistaken, according to Table 2, the following predictors are not significant: Age, GSI score, number of symptoms of dependent personality disorder. It seems that the impact of number of symptoms of avoidant personality disorder is higher than the impact of number of symptoms of conduct disorder. What happened to the predictor "Passive-aggressive personality disorder"?

- We are very sorry about this inconsistency. We have checked the results from the new analysis.

Table 2 is missing 95% confidence intervals of the hazard ratios, as well as regression weights, standard errors of regression weights and degrees of freedom. Should "probability" mean the significance level (p value) of the tests for the different predictors? Names of predictors should be as precise as possible, e.g. 'number of drugs' instead of 'drugs in urine'. 'Drugs in urine' could also refer to a binary categorical variable.

- We have now provided the hazard ratios with confidence intervals. We have also added the Wald statistic and a “number of drugs in urine”.

- The coefficients can easily be calculated based on these, simply by calculating the natural logarithm of the figure given. Degrees of freedom are given for the overall regression model, but other than that, we failed to find any references to the degrees of freedom for individual parameters.

Results, Figure 1: The figure caption should be more detailed. In its current state the figure is not self-explanatory. If I am not mistaken, Kaplan-Meier curves estimate cumulative survival probability, not proportions. In the case of this study, the probability may be called cumulative abstinence probability or retention probability; the time-to-event would be accordingly time-to-relapse or time-to-discharge because death is not the event of outcome. Do the three survival curves differ statistically significantly from each other?

- We were a bit uncertain about the difference between probability and proportion in this particular context. The figure shows the unadjusted cumulative proportion surviving, and is only given for illustrative purposes. Therefore, we did not assess whether the particular curves were statistically significant, as this analysis would be redoing the regression
analysis, but with the loss of information associated with cut-offs, as well as without the information from adjusting for covariates.

Discussion, page 12: "Even so, the patients with more severe antisocial personality traits were at increased risk of dropping out of treatment." How did you measure severity of traits? If I am not mistaken, the predictor was number of symptoms.

- Dr. Krampe is right. We used number of symptoms, and this is how we dimensionally assessed severity of conduct disorder. This has been explicated.

Discussion, page 12: "Patients with avoidant personality disorder traits …" This term would refer to the categorical variable 'Patients with versus without avoidant personality traits". If I am not mistaken, the predictor was number of symptoms of avoidant personality disorder.

- This is true. The section has been removed, due to Dr. Krampe’s other suggestion.

Discussion, page 13: "In contrast with previous studies, we did not find that sense of coherence predicted substance use outcomes. The reasons for this difference are not clear." Was there also no significant prediction of time-to-discharge when SOC was the only covariate of Cox regression analysis or when it was included in smaller sets of predictor variables? SOC has normally moderate to strong associations with measures of psychiatric distress. Perhaps it would show impact on outcome in a regression model that does not include the GSI as covariate.

- While this has been omitted from the final analysis, we did test this. It was not significant.

Discussion, page 13: "Self-reported symptoms were independently associated with higher risk of involuntary discharge. Previous research has been mixed concerning the impact of depression and anxiety on involuntary discharge". What does this interpretation mean? Do you refer to SCID screening data, GSI, or the SCL-90-R depression and anxiety subscales? How does the statement fit to Table 2? From which variables were self-reported symptoms independently associated?

- This was referring to the SCL-90, but it has been reworded

Discussion, page 13: "The use of well-validated instruments to assess personality …" see comments to Methods, SCID-II screening questionnaire, as well as to statistical analyses.
• Even though other instruments could have been useful, we still think we have arguments to support the validity of the conduct disorder criteria count.

Discussion, page 14, Conclusion: "Patients who…have a history of serious conduct disorder." To support this conclusion, the categorical variable "Conduct disorder yes versus no" needs to show a significant impact on outcome. Do the survival curves in Figure 1 differ statistically significantly from each other?

• This has been reworded. Comparing the survival curves would not make much sense, as it would be doing the same analysis this time replace the dimensional (powerful) model with a less powerful method that randomly divide the group into those with low, medium and high severity, and comparing the three.