

ORIGINAL ARTICLE

Personality disorder and functioning in major depressive disorder: a nested study within a randomized controlled trial

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Objective: This study aimed to determine if personality disorder (PD) predicted functional outcomes in patients with major depressive disorder (MDD).

Methods: Data (n=71) from a double-blind, randomized, placebo-controlled 12-week trial assessing the efficacy of 200 mg/day adjunctive minocycline for MDD were examined. PD was measured using the Standardized Assessment of Personality Abbreviated Scale. Outcome measures included Clinical Global Impression – Improvement (CGI-I), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Social and Occupational Functioning Scale (SOFAS), and Range of Impaired Functioning (RIFT). Analysis of covariance was used to examine the impact of PD (dichotomized factor [≥ 3] or continuous measure) on the outcome measures-treatment group correlation.

Results: PD was identified in 69% of the sample. After adjusting for age, sex, and baseline scores for each of the outcome measures, there was no significant difference between participants with and without PD on week 12 scores for any of the outcome measures (all $p > 0.14$).

Conclusion: In this secondary analysis of a primary efficacy study, PD was a common comorbidity among those with MDD, but was not a significant predictor of functional outcomes. This study adds to the limited literature on PD in randomized controlled trials for MDD.

Clinical trial registration: ACTRN12612000283875.

Keywords: Personality disorders; depression; clinical trial

Introduction

Randomized controlled trials (RCTs) have demonstrated that psychological and pharmacological interventions are efficacious in the treatment of depression. While these therapies have generally indicated their usefulness, it is estimated that as many as 40-70% of patients either do not respond adequately or do not reach remission from use of these interventions.¹⁻³ This has led to an increased interest in understanding diverging treatment responses

between patients, with personality factors being a prospective contributor to treatment responses.

Personality disorder (PD) refers to an individual's personality structure that precludes attainment of adaptive solutions to universal life tasks.⁴ These experiences are reflected in disordered cognition, affectivity, interpersonal and occupational functioning, and impulse control.⁵ PD has the potential to hinder therapeutic alliance⁶ and adherence,⁷ which are crucial determinants of treatment outcome. In one RCT for patients with major

depressive disorder (MDD), therapeutic alliance was found to predict response to both placebo and antidepressant medication.⁸ As such, appreciation of the potential influence of personality traits and pathology in depression may enhance treatment response.

Previous research has demonstrated that MDD is strongly associated with PD. It is estimated that ~40-50% of inpatients and ~30% of outpatients with depression also meet diagnostic criteria for at least one PD.⁹⁻¹² However, in a review, Corruble et al.¹³ reported prevalence rates as high as 50-85% in outpatients where PD was measured using standardized interviews (e.g., the Structured Interview for DSM Personality Disorders [SIDP],¹⁴ Personality Assessment Form [PAF],¹⁵ and International Personality Disorder Exam [IPDE]¹⁶). The ancillary co-occurrence of PD leads to increased disease burden and number of lives lost due to disability in depression,¹⁷ though research findings in this area are mixed. Mulder,¹⁸ in a review, found that well designed studies (where treatment was controlled and randomly assigned and PD was assessed via structured clinical interview) did not show any significant difference in treatment outcome between those with comorbid PD and depression and those with depression only. Other studies^{19,20} have also reported no difference between individuals with or without PD. Conversely, in a meta-analysis, Newton-Howes et al.²¹ concluded that the co-occurrence of PD and depression doubled the risk of poor outcome, which was independent of the depression measure used. The authors, however, did not report whether or not the tools used to measure PD were diagnostic, a factor that might be pertinent to the findings.

Other research suggests that PD contributes, at least partially, to the limited therapeutic efficacy of both psychological²² and pharmacological²³ treatments in depression. For example, Tyrer et al.²⁴ reported that pharmacological therapy was more efficacious in patients with comorbid PD (measured by the Personality Assessment Schedule [PAS]²⁵) and depression than psychological therapy, which had better outcomes for patients with depression alone. Levenson et al.²⁶ reported no significant difference between interpersonal therapy and escitalopram for patients who had unipolar depression and PD (measured by the Structured Clinical Interview for DSM Axis II Disorders [SCID-II]²⁷). However, high dimensional scores of personality pathology were associated with longer time to remission, with borderline PD traits accounting for the majority of this effect.²⁶

Understanding the relationship between PD and treatment response permits extrication of clinically relevant outcomes from distinctive interventions and treatment modalities. Additionally, investigating the possible effects of PD on depression may contribute to providing more targeted treatments, leading to better outcomes. To date, research has yielded mixed results, and this has largely been due to methodological insufficiencies. The current study is nested within the context of an RCT that assessed the therapeutic efficacy of adjunctive minocycline as a treatment for MDD. Briefly, the original study was a double-blind, placebo-controlled design, where participants were assigned to receive 200 mg day of adjunctive minocycline or matched placebo for 12-weeks, with

a 16-week follow-up phase.²⁸ The results demonstrated no significant differences in depression scores on the Montgomery Asberg Depression Rating Scale (MADRS)²⁹ (primary outcome) between groups at week 12. Secondary outcomes, including measures of functioning and quality of life, however, demonstrated significant improvement in the adjunctive minocycline group at the end of the treatment and follow-up phases. Small to large effect sizes were observed, with the largest effect sizes seen in improvement in clinical impressions and general functioning.

The aim of this study was to determine whether PD predicts functional outcomes in a group of participants with MDD who participated in a double-blind, randomized, placebo-controlled trial. It was hypothesized that participants with comorbid PD and depression would have poorer functional outcomes compared to participants without comorbid PD.

Method

Study design

Data were pooled from a double-blind, randomized, placebo-controlled 12-week trial evaluating the efficacy of 200 mg per day adjunctive minocycline for MDD.^{28,30} The original efficacy trial conformed to Good Clinical Practice (GCP) guidelines and was approved by the applicable human research and ethics committees. The study was registered in the Australian and New Zealand Clinical Trials registry: #ACTRN12612000283875.

Participants

Detailed characteristics of the sample have been described previously.^{28,30} Briefly, a total of 71 participants completed the 12-week trial, of which 47 were female (mean age [M^{age}] 52.8, standard deviation [SD] 12.3 years) and 24 were male (M^{age} 47.8, SD 15.5 years), all of whom were included in this study. Participants were recruited across three sites, two in Victoria, Australia, and one in Bangkok, Thailand, via community advertisement and referral from private and public health sectors. All participants were outpatients and remained on treatment as usual. After informed consent was given, the participants attended clinical interviews every 2 to 4 weeks throughout the trial. A post-discontinuation interview was conducted 4-weeks post-treatment cessation. Eligibility was contingent on the DSM-IV criteria of the Mini International Neuropsychiatric Interview Plus (MINI-PLUS) 5; a baseline score of ≥ 25 on the MADRS; and if applicable, stable antidepressant treatment for at least 2 weeks prior to randomization. Participants were randomly assigned according to guidelines for the Consolidated Standards of Reporting Trials (CONSORT) by means of block permutations.

Study monitoring and safety

The participants' psychotropic medication use at baseline and follow-up visits were documented. Adverse events were documented and reviewed by the principal

investigator. Treatment compliance was calculated via pill count and self-reporting. Inter-rater reliability was determined at 6-month intervals.

Outcome measures

PD was measured using the Standardized Assessment of Personality – Abbreviated Scale (SAPAS), which was administered at week 4 (to decrease participant burden at the baseline interview). The SAPAS is a validated eight-item screening measure used to assess the presence of PD in clinical populations. Participants dichotomously indicate whether they endorse a personality item in general. Summed scores range from 0-8, with a cutoff of ≥ 3 , indicating the presence of PD. The SAPAS has demonstrated moderate longer-term stability (test-retest intraclass correlation 0.58),³¹ and good sensitivity (0.73) and specificity (0.85) with the SCID-II, with a total score of 3 correctly identifying PD in 90% of participants.³² Subsequent validation studies have also shown utility in using a cutoff score of 3 as an indicator of the presence of PD in clinical populations, including patients with depression.³³

Clinical impressions were measured with the Clinical Global Impression – Improvement (CGI-I) scale.³⁴ The CGI-I is a seven item clinician-rated scale used to measure changes in illness presentation at the time of assessment, compared to the patient's presentation at baseline.

Functioning was assessed using both clinician-assessed and self-report measures. The Social and Occupational Functioning Scale (SOFAS)³⁵ is a 100-point clinician-rated tool used to measure a person's difficulty in social and occupational functioning. The SOFAS consists of 10 intervals and is scored by determining an individual's level of functioning in work and study, personal and social relationships, self-care, and disturbing and aggressive behavior. The Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT)³⁶ is a brief measure of functional impairment whereby clinicians determine the extent to which psychopathology specifically impairs functioning in four domains. The domains are comprised of work (i.e., employment, household activities, and studies), interpersonal relationships (i.e., spouse, children, and other relatives), life satisfaction, and recreation. Higher scores on each domain reflect greater impairment, and each domain is then summed to yield a total score.

Self-reported quality of life was measured using the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF).³⁷ The Q-LES-Q-SF is a 16-item tool, where participants indicate how satisfied they are with their areas of life functioning on a five-point scale, which ranges from very poor to very good. The first 14 items of the Q-LES-Q-SF are summed to yield a total raw score, with the final two items being stand-alone scores.

Statistical analysis

All statistical analyses were performed using SPSS version 24. Analyses were conducted on randomized participants who had completed at least one post-baseline interview (modified intention-to-treat protocol). Statistical threshold

was set at the 95% confidence level. Baseline characteristics were compared using *t*-test and chi-square test analyses. To examine the impact of PD on outcome measures (i.e., CGI-I, Q-LES-Q-SF, SOFAS, and LIFE-RIFT), time by treatment interactions were examined in a model that comprised the fixed categorical effects of PD, treatment, and PD by treatment interaction.

Analysis of covariance (ANCOVA) was completed to examine the impact of PD (both as a dichotomized factor or a continuous measure) on outcome measures-treatment group correlation. The mediator variable was personality (i.e., PD or not, or continuous SAPAS score) and the independent variable was treatment allocation (i.e., minocycline or placebo). Each outcome measure was explored as the change from baseline to week 12 (i.e., CGI-I, LIFE-RIFT, SOFAS, Q-LES-Q-SF). Two-way interaction of PD and treatment allocation was tested for, examining the effect modification of PD status or personality score, in addition main effect of PD status or personality score was tested as modifier non-specified predictor. Effect sizes were also examined for each analysis.

Results

A total of 69% of the sample met criteria for PD ($M = 3.44$, $SD = 1.90$). Baseline demographic characteristics of participants with and without PD are shown in Table 1. Those with a PD were more likely have a self-reported psychiatric comorbidity and past history of dysthymia; otherwise the groups were similar in regards to age, sex, treatment allocation, psychiatric history, self-reported psychiatric comorbidity, medication use, and baseline symptom status and functioning. Table 2 shows the endorsement of each SAPAS item. No significant differences were found for MADRS responders (defined by $\geq 50\%$ reduction in scores from baseline to week 12; $p = 0.35$) and remitters (defined by MADRS week 12 score of < 7 ; $p = 0.14$) according to patients with PD (responders 37.8%; remitters 18.9%) and without PD (responders 40%; remitters 16.7%). After adjusting for age, sex, and baseline outcome measure scores, there was no significant difference between participants with and without PD in week 12 scores (Table 3) for CGI-I ($F_{1,53} = 0.30$, $p = 0.59$, partial eta squared = 0.01); LIFE-RIFT ($F_{1,53} = 0.05$, $p = 0.83$, partial eta squared = < 0.001); SOFAS ($F_{1,53} = 0.01$, $p = 0.94$, partial eta squared = < 0.001); Q-LES-Q-SF: ($F_{1,66} = 0.01$, $p = 0.95$, partial eta squared = < 0.001). Additionally, no significant difference was found when PD was entered as a continuous covariate into the analysis: CGI-I ($F_{1,53} = 1.17$, $p = 0.28$, partial eta squared = 0.02); LIFE-RIFT ($F_{1,53} = 0.06$, $p = 0.81$, partial eta squared = < 0.001); SOFAS ($F_{1,53} = 0.09$, $p = 0.76$, partial eta squared = < 0.001); Q-LES-Q-SF ($F_{1,66} = 0.15$, $p = 0.70$, partial eta squared = < 0.001).

Discussion

In this nested study, PD, as measured by the SAPAS, was a common comorbidity in this sample of participants with depression. It was found that PD was not a significant

Table 1 Baseline demographic characteristics of participants with and without PD

| | PD (n=49) | No PD (n=22) | p-value |
|---|-------------|--------------|-------------|
| Age, mean (SD) | 50.2 (15.0) | 47.8 (14.2) | 0.67 |
| Female, n (%) | 31 (66.0) | 16 (34.0) | 0.44 |
| BMI, mean (SD) | 28.0 (5.2) | 25.9 (5.6) | 0.13 |
| Treatment allocation (randomized to minocycline group), n (%) | 24 (48.9) | 25 (51.0) | 0.66 |
| Psychiatric history | | | |
| Duration of illness (years since depression diagnosis), mean (SD) | 13.5 (12.1) | 15.1 (13.7) | 0.27 |
| Depression symptom onset (years), mean (SD) | 25.0 (14.0) | 29.0 (14.9) | 0.28 |
| Number of hospitalizations, mean (SD) | 0.51 (1.34) | 1.32 (2.1) | 0.15 |
| Number of depressive episodes, median (range)* | 1.0 (1-5) | 2.0 (1-5) | 0.28 |
| Suicide attempts, n (%) | 18 (36.7) | 9 (40.1) | 0.74 |
| Psychiatric comorbidity (self-report), n (%) | 33 (67.3) | 8 (36.4) | 0.02 |
| Psychiatric comorbidity (MINI-5), n (%) | | | |
| MDE current | 49 (100.0) | 22 (100.0) | - |
| MDE past | 46 (93.9) | 19 (86.4) | 0.29 |
| MDD with melancholia | 35 (71.4) | 17 (77.3) | 0.61 |
| Dysthymia current | 12 (24.5) | 4 (18.2) | 0.56 |
| Dysthymia past | 27 (55.1) | 6 (27.3) | 0.03 |
| Suicidality risk (total) – current | 28 (57.1) | 14 (63.6) | 0.61 |
| Anxiety disorders (pooled) – current [†] | 30 (61.2) | 11 (50.0) | 0.38 |
| Alcohol dependence (pooled) [‡] | 8 (16.3) | 5 (22.7) | 0.55 |
| Alcohol abuse (pooled) [§] | 3 (6.1) | 5 (22.7) | 0.25 |
| Substance use (pooled) | 1 (2.0) | 0 (0.0) | 0.50 |
| Baseline medications (yes/no), n (%) | | | |
| Antidepressant | 46 (93.8) | 18 (81.8) | 0.12 |
| Complimentary | 25 (51.0) | 10 (45.5) | 0.66 |
| Benzodiazepines | 16 (32.7) | 7 (31.8) | 0.95 |
| Antipsychotic | 10 (20.4) | 2 (9.1) | 0.24 |
| Pain | 10 (20.4) | 3 (13.6) | 0.50 |
| Mood stabilizer | 4 (8.2) | 3 (13.6) | 0.47 |
| Other | 30 (61.2) | 13 (59.1) | 0.87 |
| Baseline symptom status and functioning, mean (SD) | | | |
| MADRS | 31.4 (4.0) | 31.5 (5.0) | 0.67 |
| CGI-I (from week 2) | 4.6 (0.76) | 4. (0.83) | 0.50 |
| LIFE-RIFT | 14.1 (2.9) | 13.8 (2.42) | 0.67 |
| SOFAS | 57.2 (10.1) | 57.1 (9.17) | 0.70 |
| Q-LES-Q-SF | 41.6 (13.1) | 40.5 (11.2) | 0.75 |

BMI = body mass index; CGI-I = Clinical Global Impression – Improvement; GAD = generalized anxiety disorder; LIFE-RIFT = Range of Impaired Functioning Tool; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; MINI-5 = Mini International Psychiatric Interview; OCD = obsessive-compulsive disorder; PD = personality disorder; Q-LES-Q-SF = Quality of Life and Enjoyment Satisfaction Questionnaire – Short Form; SD = standard deviation; SOFAS = Social and Occupational Functioning Scale.

* Category 1 = 1-5; category 2 = 5-10 previous depressive episodes.

[†] Pooled anxiety disorders include: agoraphobia with/without history of panic disorder/without history of limited symptom attacks, social anxiety disorder, OCD, OCD due to a general medical condition, substance induced OCD, post-traumatic stress disorder, GAD, GAD due to general medical condition, substance-induced GAD.

[‡] Pooled alcohol dependence includes: current and past dependence.

[§] Pooled alcohol abuse includes: current and past abuse.

^{||} Pooled substance use includes: current and lifetime dependence.

Table 2 Frequency of Standardized Assessment of Personality – Abbreviated Scale (SAPAS) item endorsement

| SAPAS item | |
|---|-----------|
| In general do you have difficulty making and keeping friends? | 34 (13.9) |
| Would you normally describe yourself as a loner? | 39 (16.0) |
| In general do you trust other people?* | 26 (10.7) |
| Do you normally lose your temper easily? | 18 (7.4) |
| Are you normally an impulsive sort of person? | 24 (10.0) |
| Are you normally a worrier? | 54 (22.1) |
| In general, do you depend on others a lot? | 12 (4.9) |
| In general, are you a perfectionist? | 37 (15.2) |

Data presented as n (%) based on 244 endorsed items.

* Reverse coded.

predictor of functional outcomes. Thus, functional outcomes were not differently experienced by those with comorbid PD.

To date, relatively few RCTs have considered the influence of PD on the relationship between depression, the intervention being assessed, and associated outcomes. Comparable to our findings, in a systematic review examining the relationship between personality (traits and disorder), depression, and treatment outcomes, Mulder¹⁸ also found no difference between those with or without co-occurring PD. Robustly designed studies, which included assessment of PD using structured clinical interviews (e.g., SIDP, SCID, and IPDE) and either

Table 3 Outcome measures at week 12 based on analysis of covariance (n=71)

| | Minocycline | | | | Placebo | | | | PD dichotomized | | | PD continuous | | |
|------------|---------------|----|---------------|----|---------------|----|---------------|----|-----------------|------|---------|---------------|------|---------|
| | PD | | No PD | | PD | | No PD | | χ^2 | F | p-value | χ^2 | F | p-value |
| | Mean (SD) | n | | | | | | |
| MADRS | 14.42 (8.90) | 19 | 20.38 (11.86) | 8 | 18.86 (9.77) | 22 | 20.56 (12.55) | 9 | 219.76 | 2.23 | 0.14 | 14.16 | 0.14 | 0.71 |
| CGI-I | 2.50 (1.41) | 8 | 2.25 (1.21) | 20 | 3.56 (1.42) | 9 | 2.90 (1.21) | 20 | 0.49 | 0.30 | 0.59 | 1.87 | 1.17 | 0.28 |
| LIFE-RIFT | 11.00 (4.81) | 8 | 10.30 (2.94) | 20 | 12.56 (3.53) | 9 | 12.33 (3.81) | 21 | 0.50 | 0.05 | 0.83 | 0.57 | 0.06 | 0.81 |
| SOFAS | 69.00 (17.58) | 8 | 68.70 (11.26) | 20 | 62.78 (16.21) | 9 | 65.05 (14.52) | 21 | 0.66 | 0.01 | 0.94 | 12.00 | 0.09 | 0.76 |
| Q-LES-Q-SF | 37.00 (31.92) | 12 | 42.83 (23.66) | 24 | 38.10 (21.36) | 10 | 41.44 (23.83) | 35 | 2.69 | 0.01 | 0.95 | 83.33 | 0.15 | .070 |

CGI-I = Clinical Global Impression – Improvement; LIFE-RIFT = Range of Impaired Functioning Tool; MADRS = Montgomery-Åsberg Depression Rating Scale; PD = personality disorder; Q-LES-Q-SF = Quality of Life and Enjoyment Satisfaction Questionnaire – Short Form; SD = standard deviation; SOFAS = Social and Occupational Functioning Scale.

controlled for standard treatment or randomly assigned participants to treatment groups, did not show any significant difference in treatment outcome between individuals with or without PD. However, studies that used less robust methods to measure PD (e.g., clinician-rated assessments and interview-informant standardized interviews) yielded mixed results, with some studies reporting individuals with PD traits have a reduced likelihood to respond to treatment and that treatment responders had fewer PD traits. Methodological differences between these studies did not allow meta-analysis.¹⁸ While there are important differences between this study and the aforementioned findings, namely that PD was determined using a brief screening tool, MDD was assessed with the aid of structured clinical interviews, and functional outcomes were the primary objective of the current study, in line with the findings of Mulder.¹⁸ Additionally, the current findings are akin to those put forward by Kool et al.,¹⁹ who, in a meta-analysis of RCTs, found that comorbid PD (measured via validated, structured interview) did not negatively affect pharmacological treatment outcome.

The prevalence of PD was common in this sample of participants with depression, with 69% of the sample having a comorbid PD. This result is comparable to what has been reported in other studies. For instance, Hasin et al.,⁹ in a national community-based sample of adult residents in the United States, found that the 12-month prevalence rate of PD (measured by structured diagnostic interview) was 37.9%. Unger et al.,¹¹ in an inpatient sample, found that PD prevalence, assessed by the SCID-II, was 40.5%. Zimmerman et al.¹² reported prevalence rates of 45.5% in an outpatient sample measured by the SIDP-IV. Given the common comorbidity reported, PD may play a role, if not in relation to functional or treatment outcome, then potentially for other areas which affect treatment, such as therapeutic alliance, disease progression, recurrence, or requirement for adjunctive therapies.²⁶

Previous research^{38,39} has identified that successful treatment of depression is related to improvement in measures of PD. This may be an important confounder of the current study, as these data were not collected. In particular, depression may exacerbate or unmask overt PD features, and thus lend itself to high rates of co-occurring PD. Systematic inflammation may also play a role in the pathogenesis of PD. For example, Osimo et al.⁴⁰ found that the prevalence rate of low-grade systematic inflammation (serum C reactive protein [CRP] level > 3 mg/L) was 42% in an inpatient sample. Wium-Andersen et al.,⁴¹ in a large community based sample, found that increasing CRP levels (1.01-3.00, 3.01-10.00, and > 10.00 mg/L) were associated with increased risk of depression and psychological distress. Although examination of inflammatory markers was beyond the scope of the current study, it may be that the similarity in psychiatric profiles between participants with and without PD reflects comparable inflammatory profiles, and thus did not yield a significant difference in measures of functioning.

The most frequently endorsed SAPAS items in the current study are noteworthy. Specifically, “Are you normally a worrier?,” “Would you normally describe yourself as a loner?,” and “In general are you a perfectionist?.”

These items appear to be representative of individuals with cluster C PD (i.e., avoidant, dependent, obsessive-compulsive). The DSM-5 denotes that individuals with cluster C PD may appear anxious or fearful.⁵ In particular, individuals with avoidant PD are described as displaying patterns of social inhibition and hypersensitivity to negative evaluation; those with dependent PD have difficulty making everyday decisions and require excessive advice and reassurance from others; and individuals with obsessive-compulsive PD display preoccupation with perfectionism, orderliness, and mental and interpersonal control.⁴¹ Previous literature has identified that those with cluster C PD and depression experience worse pre-treatment functioning⁴² and depression severity⁴³ than patients with depression alone.

Furthermore, there is evidence to suggest that patients with cluster C PD are considerably more likely to seek treatment than individuals with cluster A (i.e., paranoid, schizoid, schizotypal; who typically reject treatment), or cluster B (i.e., antisocial, histrionic, borderline, narcissistic; who display both treatment seeking and rejecting qualities) PD.^{44,45} However, those with cluster C PD often seek treatment for the comorbid psychiatric condition/s, in which their underlying PD has not previously been diagnosed or treated, eventually leading to recurrence of the additional psychiatric condition.⁴⁶ Given that the RCT in the current study was adjunctive to treatment as usual, participants are likely to be patients who endure recurrent episodes of MDD and participate in RCTs to pursue the potential of improved wellbeing. As such, the high prevalence but non-significant results may reflect an over-representation of participants with cluster C PD (who function adequately, but experience considerable personal distress), and thus seek additional psychiatric treatment (in this case, adjunctive treatment for MDD).

The current study is not without limitations. Firstly, PD was measured via screening assessment, rather than structured clinical interview. This assessment method did not allow for the breakdown of specific PDs, which may have provided useful information pertinent to the current findings. It is likely that this study captured participants of the cluster C PD category and was under-represented by patients with cluster A or B PDs. Moreover, PD was measured at one time-point only. As such, it is not known if endorsement of PD items changed over time in accordance with improvement in functioning. However, previous literature has identified that PD has high diagnostic stability over time.^{47,48} Secondly, the primary efficacy study was not significant even though key secondary outcomes were positive. As such, differences between treatment outcomes for participants with and without PD could not be robustly ascertained, and this would limit the capacity to detect mediators of response. Thirdly, the sample size of the original RCT offered limited power to deduce definitive assertions about the primary outcome. Finally, multiple comparisons were not corrected for, which may have increased the chances of type 1 error.

Notwithstanding these limitations, this study provides useful data on the prevalence of PD in patients with co-occurring MDD. Historically, it has been commonplace for RCT designs to either exclude patients with PD or omit

the measurement of PD entirely, despite the high comorbidity of these disorders. These data show that although PD was highly prevalent in this sample, PD did not appear to have any clear effect on the functional outcomes that were assessed. To clarify the effect on functional outcomes, future studies should assess the presence and impact of patients with PD. Moreover, the clinical implications of these data suggest that patients with PD may be treated by minocycline in the same way as patients without PD, though the efficacy of minocycline in the treatment of depression warrants further investigation. In summary, the current study adds to the lack of evidence pertaining to the functional outcomes of PD in patients with MDD in an RCT setting.

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References

- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905-17.
- Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*. 2005;66:974-81.
- Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, et al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry*. 2005;62:417-22.
- Livesley JW. An empirically-based classification of personality disorder. *J Pers Disord*. 2011;25:397-420.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Arlington: American Psychiatric Publishing; 2013.
- Bordin ES. The generalizability of the psychoanalytic concept of the working alliance. *Psychol Psychother-T*. 1979;16:252-60.
- Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in individual psychotherapy. *Psychotherapy (Chic)*. 2011;48:9-16.
- Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. *Br J Psychiatry*. 2014;205:443-9.
- Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the national epidemiologic survey on alcoholism and related conditions. *Arch Gen Psychiatry*. 2005;62:1097-106.
- Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the wave 2 national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry*. 2008;69:533-45.
- Unger T, Hoffmann S, Kohler S, Mackert A, Fydrich T. Personality disorders and outcome of inpatient treatment for depression: a 1-year prospective follow-up study. *J Pers Disord*. 2013;27:636-51.
- Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. *Am J Psychiatry*. 2005;162:1911-8.
- Corruble E, Gineestet D, Guelfi JD. Comorbidity of personality disorders and unipolar major depression: a review. *J Affect Disord*. 1996;37:157-70.
- Pfohl B, Stangl D, Zimmerman M. *Structured interview for DSM-III personality disorders*. 2nd ed. Iowa City: University of Iowa, College of Medicine; 1983.
- Shea MT. *Personality assessment form*. Providence: Brown University School of Medicine, Department of Psychiatry and Human Behavior; 1989.
- Loranger AW, Susman VL, Oldham JM, Russakoff LM. The personality disorder examination: a preliminary report. *J Pers Disord*. 1987;1:1-13.
- Friborg O, Martinsen EW, Martinussen M, Kaiser S, Overgard KT, Rosenvinge JH. Comorbidity of personality disorders in mood disorders: a meta-analytic review of 122 studies from 1988 to 2010. *J Affect Disord*. 2014;152-154:1-11.
- Mulder RT. Personality pathology and treatment outcome in major depression: a review. *Am J Psychiatry*. 2002;159:359-71.
- Kool S, Schoevers R, de Maat S, Van R, Molenaar P, Vink A, et al. Efficacy of pharmacotherapy in depressed patients with and without personality disorders: a systematic review and meta-analysis. *J Affect Disord*. 2005;88:269-78.
- Russell JM, Kornstein SG, Shea MT, McCullough JP, Harrison WM, Hirschfeld RM, et al. Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *J Clin Psychiatry*. 2003;64:554-61.
- Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: meta-analysis of published studies. *Br J Psychiatry*. 2006;188:13-20.
- Spek V, Nyklicek I, Cuijpers P, Pop V. Predictors of outcome of group and internet-based cognitive behavior therapy. *J Affect Disord*. 2008;105:137-45.
- T Mulder R. The influence of personality on the treatment outcome of psychopathology. *World Psychiatry*. 2011;10:115-6.
- Tyrer P, Seivewright N, Ferguson B, Murphy S, Johnson AL. The Nottingham study of neurotic disorder. Effect of personality status on response to drug treatment, cognitive therapy and self-help over two years. *Br J Psychiatry*. 1993;162:219-26.
- Tyrer P, Alexander J. Personality assessment schedule. In: Tyrer P. *Personality disorders: diagnosis, management and course*. Kent: Wright/Butterworth Scientific; 1988. p. 43-62.
- Levenson JC, Wallace ML, Fournier JC, Rucci P, Frank E. The role of personality pathology in depression treatment outcome with psychotherapy and pharmacotherapy. *J Consult Clin Psychol*. 2012;80:719-29.
- First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. *Structured clinical interview for DSM-IV axis II personality disorders (SCID-II)*. Washington: American Psychiatric Press; 1997.
- Dean OM, Kanchanatawan B, Ashton M, Mohebbi M, Ng CH, Maes M, et al. Adjunctive minocycline treatment for major depressive disorder: a proof of concept trial. *Aust N Z J Psychiatry*. 2017;51:829-40.
- Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-9.
- Dean OM, Maes M, Ashton M, Berk L, Kanchanatawan B, Sughondhabrirom A, et al. Protocol and rationale-the efficacy of minocycline as an adjunctive treatment for major depressive disorder: a double blind, randomised, placebo controlled trial. *Clin Psychopharmacol Neurosci*. 2014;12:180-8.
- Hesse M, Rasmussen J, Pedersen MK. Standardised assessment of personality – a study of validity and reliability in substance abusers. *BMC Psychiatry*. 2008;8:7.
- Moran P, Leese M, Lee T, Walters P, Thornicroft G, Mann A. Standardised Assessment of Personality – Abbreviated Scale (SAPAS): preliminary validation of a brief screen for personality disorder. *Br J Psychiatry*. 2003;183:228-32.
- Hesse M, Moran P. Screening for personality disorder with the Standardised Assessment of Personality: abbreviated Scale (SAPAS): further evidence of concurrent validity. *BMC Psychiatry*. 2010;10:10.
- Guy W, National Institute of Mental H, Psychopharmacology Research B, Early Clinical Drug Evaluation P. *ECDEU assessment manual for psychopharmacology*. Rockville: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
- Morosini P, Magliano L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV social and occupational functioning assessment scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101:323-9.
- Leon AC, Solomon DA, Mueller TI, Turvey CL, Endicott J, Keller MB. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. *Psychol Med*. 1999;29:869-78.
- Stevanovic D. Quality of Life Enjoyment and Satisfaction Questionnaire – short form for quality of life assessments in clinical

- practice: a psychometric study. *J Psychiatr Ment Health Nurs*. 2011; 18:744-50.
- 38 Hirschfeld RM, Klerman GL, Clayton PJ, Keller MB, McDonald-Scott P, Larkin BH. Assessing personality: effects of the depressive state on trait measurement. *Am J Psychiatry*. 1983;140:695-9.
- 39 Keller MB, Gelenberg AJ, Hirschfeld RM, Rush AJ, Thase ME, Kocsis JH, et al. The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. *J Clin Psychiatry*. 1998;59:598-607.
- 40 Osimo EF, Cardinal RN, Jones PB, Khandaker GM. Prevalence and correlates of low-grade systemic inflammation in adult psychiatric inpatients: an electronic health record-based study. *Psychoneuroendocrinology*. 2018;91:226-34.
- 41 Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73,131 individuals. *JAMA Psychiatry*. 2013;70:176-84.
- 42 Renner F, Bamelis LL, Huibers MJ, Speckens A, Arntz A. The impact of comorbid depression on recovery from personality disorders and improvements in psychosocial functioning: results from a randomized controlled trial. *Behav Res Ther*. 2014;63:55-62.
- 43 Moradveisi L, Huibers MJ, Renner F, Arasteh M, Arntz A. The influence of comorbid personality disorder on the effects of behavioural activation vs antidepressant medication for major depressive disorder: results from a randomized trial in Iran. *Behav Res Ther*. 2013;51:499-506.
- 44 Tyrer P, Mitchard S, Methuen C, Ranger M. Treatment rejecting and treatment seeking personality disorders: Type R and Type S. *J Pers Disord*. 2003;17:263-8.
- 45 Eskedal GA, Demetri JM. Etiology and treatment of cluster C personality disorders. *J Ment Health Couns*. 2006;28:1-17.
- 46 Sperry L. Personality disorders. In: Sperry L, Carlson I. *Psychopathology and psychotherapy: from DSM-IV diagnosis to treatment*. 2nd ed. Washington: Accelerated Development/Taylor & Francis; 1995. p. 279-336.
- 47 Chanen AM, Jackson HJ, McGorry PD, Allot KA, Clarkson V, Yuen HP. Two-year stability of personality disorder in older adolescent outpatients. *J Pers Disord*. 2004;18:526-41.
- 48 Bukh JD, Bech P, Kessing LV. Diagnostic stability of comorbid personality disorders among patients fully or partially remitted from first-episode depression: a 5-year follow-up study. *J Pers Disord*. 2017;31:208-20.