

Key patterns and predictors of response to treatment for military veterans with post-traumatic stress disorder: a growth mixture modelling approach

A. J. Phelps^{1*}, Z. Steel², O. Metcalf¹, N. Alkemade¹, K. Kerr³, M. O'Donnell¹, J. Nursey¹, J. Cooper¹, A. Howard¹, R. Armstrong¹ and D. Forbes¹

¹Department of Psychiatry, Phoenix Australia – Centre for Posttraumatic Mental Health, University of Melbourne, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Australia

²St John of God Richmond Hospital and School of Psychiatry, University of New South Wales, Sydney, Australia

³Toowong Private Hospital, 496 Milton Road, Toowong, Queensland, Australia

Background. To determine the patterns and predictors of treatment response trajectories for veterans with post-traumatic stress disorder (PTSD).

Methods. Conditional latent growth mixture modelling was used to identify classes and predictors of class membership. In total, 2686 veterans treated for PTSD between 2002 and 2015 across 14 hospitals in Australia completed the PTSD Checklist at intake, discharge, and 3 and 9 months follow-up. Predictor variables included co-morbid mental health problems, relationship functioning, employment and compensation status.

Results. Five distinct classes were found: those with the most severe PTSD at intake separated into a relatively large class (32.5%) with small change, and a small class (3%) with a large change. Those with slightly less severe PTSD separated into one class comprising 49.9% of the total sample with large change effects, and a second class comprising 7.9% with extremely large treatment effects. The final class (6.7%) with least severe PTSD at intake also showed a large treatment effect. Of the multiple predictor variables, depression and guilt were the only two found to predict differences in response trajectories.

Conclusions. These findings highlight the importance of assessing guilt and depression prior to treatment for PTSD, and for severe cases with co-morbid guilt and depression, considering an approach to trauma-focused therapy that specifically targets guilt and depression-related cognitions.

Received 10 January 2017; Revised 23 April 2017; Accepted 3 May 2017

Key words: post-traumatic stress disorder, predictors, PTSD, treatment response, veterans.

Post-traumatic stress disorder (PTSD) can be a severe, debilitating condition, associated with significant co-morbidity and reduced quality of life (Bryant *et al.* 2010). While effective treatments are available, treatment outcomes for military veterans with PTSD have been found to be more modest than outcomes for other populations, with 30–50% of veterans not deriving clinically meaningful benefit (Steenkamp *et al.* 2015). Studies examining the efficacy of interventions for PTSD typically report mean change with little focus on potential variability in treatment responses (Steenkamp *et al.* 2015). The identification of subclasses of veterans and the variables that predict

membership of those classes would contribute to our understanding of why veterans with PTSD remain difficult to treat, provide valuable information to clinicians about those most and least likely to respond to standard treatment (Steenkamp *et al.* 2012), and pave the way for future treatment modifications based on the factors associated with poor treatment response (Elliott *et al.* 2005; Yehuda & Hoge, 2016).

Growth mixture modelling (GMM) is used to investigate classes of individuals within a group with different treatment response trajectories (Ram & Grimm, 2009). Three studies into veterans with PTSD have found significantly different treatment trajectories: two studies found sub-groups of non-responders (Elliott *et al.* 2005; Currier *et al.* 2014), while a third study found three groups of responders with dramatically varying levels of improvement (Schumm *et al.* 2013). All three studies included a limited range of predictor variables (e.g. type of trauma exposure, age, and mental and physical health) and how they

* Address for correspondence: Dr A. J. Phelps, Phoenix Australia – Centre for Posttraumatic Mental Health, Department of Psychiatry, University of Melbourne, Level 3, Alan Gilbert Building, 161 Barry Street, Carlton VIC 3053, Australia.
(Email: ajphelps@unimelb.edu.au)

This contribution has been produced using funding provided by the Department of Veterans' Affairs (DVA). However, the views expressed in the contribution do not necessarily represent the views of the Minister for Veterans' Affairs or the Department of Veterans' Affairs. The Commonwealth of Australia does not give any warranty nor accept any liability in relation to the contents of this contribution.

subsequently impacted trajectory outcomes significantly varied across studies. Two of the previous studies were based on audits of routinely collected data (Schumm *et al.* 2013; Currier *et al.* 2014), so that potential covariates for determining class membership could only be drawn from the clinical variables used for diagnostic/treatment purposes. In contrast, variables such as guilt (Stapleton *et al.* 2006), pain (Otis *et al.* 2009), dissociation, and social factors such as compensation seeking (Fontana & Rosenheck, 1998) and relationship quality (Evans *et al.* 2009) have been found to predict PTSD treatment outcomes, and as such, warrant investigation.

This study aims to investigate the patterns and predictors of response trajectory for Australian veterans who participated in hospital-based treatment for PTSD. It builds on previous studies by including a broader range of predictor variables: age, alcohol use, depression, anger, guilt, dissociation, pain, relationship functioning, and compensation seeking status.

Method

Participants were 2686 veterans and other ex-serving members of the Australian Defence Force, who participated in an accredited PTSD outpatient treatment programme funded by the Australian Department of Veterans' Affairs (DVA) between 2002 and 2015. The majority of participants (98.8%) were male. PTSD diagnosis was established using the Clinician Administered PTSD Scale (CAPS IV). In order to qualify for treatment, the veteran's PTSD had to be military-related. Treatment followed accreditation standards with components of psychoeducation, symptom management (for co-morbid problems including anxiety, anger and depression), trauma-focused therapy, graded *in vivo* exposure, substance use issues, interpersonal skills, physical health and lifestyle issues, and relapse prevention. Programmes incorporated 20–30 treatment days with 6–10 participants receiving a combination of individual and group therapy. Exclusion criteria included being currently psychotic, actively suicidal, current substance abuse or currently involved in a major life crisis. The DVA Human Research Ethics Committee approved the study.

Measures

Participants completed questionnaires at intake, discharge, 3-month and 9-month follow-up as part of the programme evaluation process. Self-reported PTSD severity was assessed using the PTSD Checklist (PCL; Blake *et al.* 1995), a 17-item scale that measures Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) PTSD symptoms

in the past month (scores range 17–85; internal consistency 0.94–0.97; Blanchard *et al.* 1996). Participants were asked to answer the PCL in relation to their most traumatic military experience. Alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT; Saunders *et al.* 1993), a 10-item scale that assesses alcohol consumption and alcohol-related problems (scores range 0–40; internal consistency 0.80–0.94; Forbes *et al.* 2004). Depression was assessed using the Hospital Anxiety and Depression Scale (HADS), which comprises two sub-scales that measure symptoms of anxiety and depression over the past week (Zigmond & Snaith, 1983). The sub-scales have seven items each with maximum scores of 21 for each sub-scale. A review of studies found that the two sub-scales had average internal reliability coefficients of 0.83 (anxiety) and 0.82 (depression; Bjelland *et al.* 2002). Anger was measured using the seven-item Dimensions of Anger Reactions (DAR) scale, which measures anger disposition directed towards others with total possible scores of 56 (internal consistency 0.91; Forbes *et al.* 2004). Veterans in a relationship completed the Abbreviated Dyadic Adjustment Scale, a seven-item scale that measures dyadic consensus, cohesion and satisfaction (internal consistency 0.75–0.80; Hunsley *et al.* 2001). Guilt and dissociation were assessed via a two-item (range 0–8) and three-item (range 0–12) scale, respectively, derived from the CAPS IV associated features questions. The internal consistency for the guilt and dissociation scales were high ($\alpha = 0.89$; $\alpha = 0.90$), item-total correlations ranged from 0.84 to 0.86 (guilt) and 0.87–0.89 (dissociation). Pain was measured via a single item from the World Health Organization Quality of Life brief scale (WHOQOL-BREF) on a scale of 1–5 (Creamer *et al.* 2002). Demographic data, including age at intake, pension status, compensation-seeking status, and employment status, were also collected from veterans. Presence of co-morbidity was determined by clinicians.

Statistical analyses

Latent growth mixture modelling (LGMM) identifies classes of individuals with similar response trajectories. LGMM with four time points provides the opportunity to model change in both linear and non-linear (quadratic) trajectories. Intercepts were allowed to vary, as the study focused on change over time (slopes), rather than the start points. Variance of slopes was constrained within each group to 0, which sets the homogeneity of growth trajectories within each class (Feng & McCulloch, 1996). Selection of the preferred model was based on statistical and practical criteria. Statistical criteria included reviewing the Bayesian

Information Criterion (BIC; Schwarz, 1978), the Sample Size Adjusted Bayesian Information Criterion (SS-BIC), and the Akaike's Information Criterion (AIC; Akaike, 1973). Entropy values range between 0 and 1, with 1 indicating perfect differentiation between classes (Ramaswamy *et al.* 1993). Finally, the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT; Lo *et al.* 2001) and the bootstrap likelihood ratio test (BLRT; Feng & McCulloch, 1996) were reviewed. A significant LMR-LRT and BLRT indicates that the current model is better fitting than the $k-1$ class model. Practical criteria for model selection included determining that each trajectory class was of sufficient size, the final solution was interpretable and theoretically coherent. Treatment effect was calculated using Cohen's d following a repeated measures t test comparing change in scores between pre-treatment and 9-month follow-up. Cohen's d scores were calculated applying Morris and DeShon's correction for the correlations between mean scores for these within-subjects repeated measures (Morris & DeShon, 2002).

Analyses were completed in Mplus version 7.11, which utilises all available data to estimate the model using full information maximum likelihood when completing analyses (Muthén & Muthén, 2004). In the first step, the unconditional model that best fit the data was defined. The most parsimonious (one-class) model was fitted first, followed by models with increasing numbers of classes. Both linear and quadratic growth mixture models were fitted to the PCL data obtained at the four time points. In the second step, we ran conditional LGMMs to identify potential predictors of the different classes.

Predictors investigated were intake measures of: age, applying for a pension, applying for a pension increase, relationship status, psychiatric co-morbidity, employment status, alcohol use, anger, depressive symptoms, guilt symptoms, and dissociation symptoms. The inclusion of predictors into the LGMM can result in minor changes to the class structure. Therefore, if multiple models in the unconditional analyses perform similarly, it is prudent to investigate them both in the conditional analyses (Jung & Wickrama, 2008).

As the data were collected from 14 different Australian sites, we also investigated symptom clustering by site. The intra-class correlation (ICC) using absolute agreement for PCL scores at intake was $ICC = 0.021$, below the 0.1 of a small effect size for ICC. The effect of the ICC on sample size indicated that we had sufficient participants to run GMM. A multivariate analysis of variance on the conditional probability of being in each class (C1–C5) at each time point with site as the factor and found no evidence of systematic bias across sites.

Table 1. Sample demographics at intake (unless stated otherwise)

| | Mean (s.d.) |
|-------------------------------------|------------------------|
| Age (at intake) | 55.92 (10.54) |
| PCL (intake) | 61.4 (11.20) |
| PCL (end treatment) | 55.15 (12.92) |
| PCL (3 months) | 54.31 (12.83) |
| PCL (9 months) | 53.17 (12.95) |
| AUDIT | 14.38 (9.73) |
| HADS – depression | 11.50 (3.69) |
| Pain (WHO item 3) | 3.45 (1.03) |
| Guilt | 7.30 (4.29) |
| Dissociation | 9.24 (5.29) |
| Co-morbid psych – number | 1.04 (0.97), range 0–8 |
| Co-morbid psych (yes) | 64.6% |
| Applying DVA pension (yes) | 42.7% |
| Applying DVA pension increase (yes) | 47.3% |
| Employment (yes) | 13.2% |
| Relationship status | |
| Single (never married) | 3.9% |
| Married | 70.1% |
| <i>De facto</i> | 6.7% |
| Separated/divorced | 17.0% |
| Widowed | 2.2% |
| Employment status | |
| Full-time | 10.2% |
| Part-time | 3.0% |
| Retired | 21.7% |
| Unemployed | 5.8% |
| Unable to work | 57.3% |

PCL, post-traumatic stress disorder checklist; AUDIT, alcohol use disorders identification test; HADS, hospital anxiety and depression scale; DVA, Australian Department of Veterans' Affairs.

Results

Table 1 provides participant demographics. The t tests and χ^2 analyses were completed on demographic variables to analyse lost to follow-up (LTFU), which were $n = 345$ by end of treatment, $n = 379$ between end of treatment and 3-month follow-up, and $n = 400$ between 3-month and 9-month follow-up. Importantly, these figures represent non-compliance with data collection rather than treatment drop out, which is very low at around 2%. Those LTFU at the end of treatment had fewer co-morbidities ($M = 0.89$) than those who remained in the study ($M = 1.10$), and were more likely to be single at intake. Those LTFU between end of treatment and 3-month follow-up were higher on dissociation at intake ($M = 10.00$) than those who remained in the study ($M = 9.06$), and again were more likely to be single at intake. Those LTFU between 3 and 9-month follow-up were higher on AUDIT

Table 2. Fit indices for the unconditional latent growth mixture model analyses

| Model tested | Log likelihood | AIC | BIC | Adjusted BIC | Entropy | LMR-LRT | BLRT |
|-----------------------------|----------------|------------|------------|--------------|---------|---------|---------|
| Linear | | | | | | | |
| 1 Class | -32 953.478 | 65 920.955 | 65 962.226 | 65 939.985 | ** | ** | ** |
| 2 Class | -32 875.931 | 65 771.861 | 65 830.819 | 65 799.046 | 0.419 | <0.0001 | <0.0001 |
| 3 Class | -32 858.087 | 65 742.174 | 65 818.819 | 65 777.514 | 0.522 | 0.1391 | <0.0001 |
| 4 Class | -32 847.794 | 65 727.589 | 65 821.922 | 65 771.085 | 0.610 | 0.2843 | <0.0001 |
| 5 Class | -32 838.806 | 65 715.612 | 65 827.632 | 65 767.263 | 0.547 | 0.2832 | <0.0001 |
| 6 Class | -32 831.737 | 65 707.475 | 65 837.183 | 65 767.282 | 0.557 | 0.0783 | <0.0001 |
| Quadratic and linear | | | | | | | |
| 1 Class | -32 761.428 | 65 538.855 | 65 586.022 | 65 560.603 | n/a | | |
| 2 Class | -32 613.609 | 65 251.219 | 65 321.969 | 65 283.841 | 0.606 | 0.0002 | <0.0001 |
| 3 Class | -32 571.899 | 65 175.798 | 65 270.131 | 65 219.294 | 0.551 | 0.5595 | <0.0001 |
| 4 Class | -32 543.494 | 65 126.988 | 65 244.904 | 65 181.358 | 0.647 | 0.0004 | <0.0001 |
| 5 Class | -32 515.419 | 65 078.838 | 65 220.338 | 65 144.082 | 0.639 | <0.0001 | <0.0001 |
| 6 Class | -32 500.613 | 65 057.226 | 65 222.308 | 65 133.344 | 0.653 | 0.0360 | <0.0001 |
| 7 Class | -32 488.466 | 65 040.932 | 65 229.598 | 65 127.924 | 0.662 | 0.2145 | <0.0001 |

AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LMR-LRT, Lo-Mendell-Rubin likelihood ratio test; BLRT, bootstrap likelihood ratio test.

Table 3. Mean scores on predictor variables by class

| Variable | Class 1 very high symptom/ small change | Class 2 very high symptom/ large change | Class 3 high symptom/ large change | Class 4 high symptom/ extra-large change | Class 5 low symptom/ large change |
|-------------|--|--|---------------------------------------|---|--------------------------------------|
| N (%) | 803 (32.5%) | 73 (3%) | 1233 (49.9%) | 196 (7.9%) | 166 (6.7%) |
| PCL Pre-tx | 66.86 | 67.28 | 59.93 | 63.13 | 43.91 |
| PCL Post-tx | 65.00 | 62.62 | 53.24 | 43.48 | 37.84 |
| PCL 3 month | 66.19 | 60.73 | 51.77 | 36.68 | 36.78 |
| PCL 9 month | 63.62 | 58.27 | 51.36 | 38.35 | 35.70 |
| Guilt | 8.62 ^{a,b} | 0.01 ^{c,d,e,b} | 7.26 ^{a,b} | 7.73 ^{a,b} | 4.05 ^{c,a,d,e} |
| Depression | 13.17 ^{d,e,b} | 11.91 ^{d,e,b} | 10.91 ^{c,a,b} | 11.22 ^{c,a,b} | 8.18 ^{c,a,d,e} |

PCL, post-traumatic stress disorder checklist; Pre-tx, pre-treatment; Post-tx, post-treatment.

^a $p < 0.05$ for reference class in table column v class 1.

^b $p < 0.05$ for reference class in table column v class 2.

^c $p < 0.05$ for reference class in table column v class 3.

^d $p < 0.05$ for reference class in table column v class 4.

^e $p < 0.05$ for reference class in table column v class 5.

scores at intake ($M = 16.04$) than those who remained ($M = 14.13$).

Tables 2 and 4 contain the full results of the unconditional LGMM analyses. Quadratic models demonstrated improved fit over linear models. As the 5 and 6 class models performed similarly in the quadratic analyses, we ran the conditional analyses with both these models before selecting the preferred model. The conditional analyses were run in two stages. Firstly, each predictor (age, applying for a pension, applying for a pension increase, relationship status,

psychiatric co-morbidity, employment status, alcohol use, anger, depressive symptoms, guilt symptoms, and dissociation symptoms) was entered into the model individually. Predictor variables were included in stage 2 if there were significant results for 50% of comparisons between classes. Following this approach, guilt, depression, dissociation, and anger were included as simultaneous predictors in stage 2.

In stage 2, the conditional LGMM was subject to model reduction and any non-significant predictors adjusting for other predictors were removed to derive

Table 4. Guilt and depression as predictors of class membership in the 5 class latent growth mixture model

| | Guilt | | Depression | |
|--|---------------|--------|---------------|--------|
| | Unstd β | p | Unstd β | p |
| Reference class : high symptom/large change | | | | |
| Low/large | -0.181 | <0.001 | -0.187 | 0.002 |
| Very high/large | -2.602 | 0.019 | 0.190 | 0.001 |
| Very high/small | 0.037 | 0.161 | 0.181 | <0.001 |
| High/extra-large | 0.025 | 0.507 | 0.018 | 0.628 |
| Reference class: low symptom/large change | | | | |
| High/large | 0.181 | <0.001 | 0.187 | 0.002 |
| Very high/large | -2.422 | 0.029 | 0.377 | <0.001 |
| Very high/small | 0.218 | <0.001 | 0.368 | <0.001 |
| High/extra-large | 0.206 | <0.001 | 0.206 | 0.006 |
| Reference class: very high symptom/large change | | | | |
| High/large | 2.602 | 0.019 | -0.190 | 0.001 |
| Low/large | 2.422 | 0.029 | -0.377 | <0.001 |
| Very high/small | 2.639 | 0.017 | -0.009 | 0.883 |
| High/extra-large | 2.627 | 0.018 | -0.171 | 0.010 |
| Reference class: very high symptom/small change | | | | |
| High/large | -0.037 | 0.161 | -0.181 | <0.001 |
| Low/large | -0.218 | <0.001 | -0.368 | <0.001 |
| Very high/large | -2.639 | 0.017 | 0.009 | 0.883 |
| High/extra-large | 0.012 | 0.767 | -0.163 | 0.001 |
| Reference class: high symptom/extra-large change | | | | |
| High/large | -0.025 | 0.507 | -0.018 | 0.628 |
| Low/large | -0.206 | <0.001 | -0.206 | 0.006 |
| Very high/large | -2.627 | 0.018 | 0.171 | 0.010 |
| Very high/small | 0.012 | 0.767 | 0.163 | 0.001 |

the most parsimonious explanation for the selected model. This process sequentially removed dissociation and anger as predictors. In the model with guilt and depression as predictors, the LMR-LRT found the 6 class model was not significantly different to the 5 class model ($p=0.2230$) and entropy was acceptable (0.639). The BLRT was significant for both the 5 class and 6 class models ($p < 0.001$). However, the 6 class solution included one excessively small class ($N \approx 1.0\%$). The 5 class model was therefore selected as the preferred model. See Table 3 for the mean PCL, guilt and depression scores for each class.

Figure 1 shows the trajectory of PCL scores for the selected LGMM conditional model with guilt and depression predicting class membership. We identified two very high-symptom classes (PCL > 67), two high-symptom classes (PCL 60–64), and one low-symptom class (PCL = 44). The two very high-symptom classes separated into a relatively large class (32.5%) with a small treatment effect size between intake and 9-month follow-up ($d=0.3$; very high-symptom/small change class) and a very small class (3%) with a large treatment effect size ($d=1.0$; very high-symptom/large change class). There were two

high-symptom classes, one comprising the largest number of participants (49.9%) showed a large treatment effect size ($d=1.6$; high-symptom/large change class) and another, comprising 7.9% of participants, showed an extremely large change ($d=2.6$; high-symptom/extra-large change class). The final class (6.7%), which started with relatively low PCL scores, showed a large treatment effect size between intake and 9-month follow-up ($d=0.9$; low-symptom/large change class).

Table 3 shows the results for guilt and depression as predictors of class membership with each class placed iteratively as the reference class. Guilt was an important predictor of outcome for participants with the most severe PTSD at intake. Amongst those with very high PTSD at intake, those with more severe guilt showed smaller treatment effects (very high-symptom/small change class), while those with lower guilt scores showed a large effect size change (very high-symptom/large change class). Depression scores, on the other hand, did not predict the small v . the large change trajectory profile of participants with very high PTSD at intake.

Neither guilt nor depression predicted class membership for those who had slightly less severe but

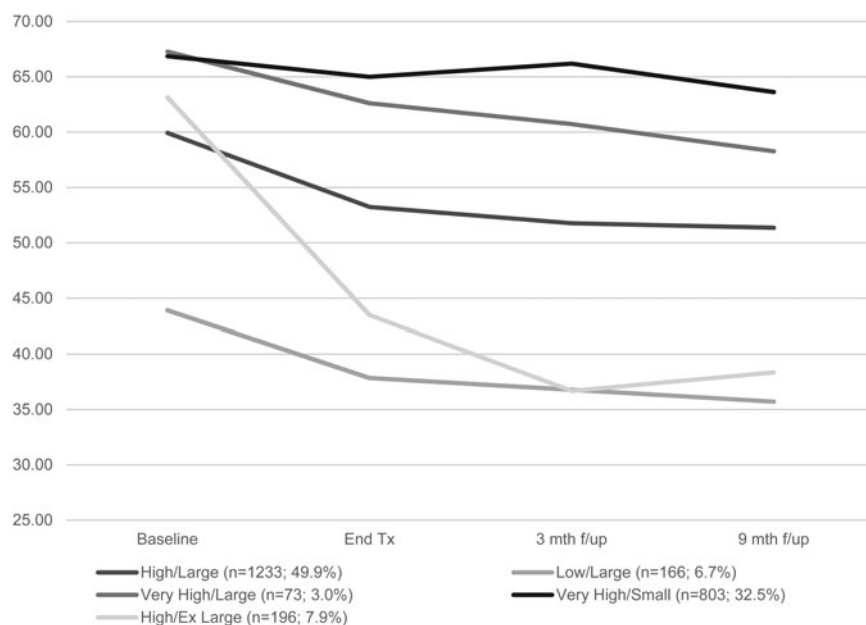


Fig. 1. Mean PCL scores for conditional 5 class latent growth mixture model with depression and guilt as predictors. PCL, post-traumatic stress disorder checklist.

still high PTSD scores at intake; as shown in Table 4, neither guilt nor depression predicted membership in the high-symptom/large change class *v.* the high-symptom/extra-large change class. The low-symptom/large change class was associated with low scores on both depression and guilt, while higher depression scores predicted being in either of the very high start classes, compared with the high-symptom/extra-large change class. Lower scores on guilt predicted being in both the low-symptom/large change and the very high-symptom/large change classes compared with the high-symptom/extra-large change class.

Post hoc analyses were run to investigate the differences in trajectories between the two very high-symptom start classes. Logistic regression analyses were run initially on each individual predictor included in the conditional LGMM procedure. Then the significant predictors were included in a backwards elimination model. The results were that alcohol use ($p = 0.018$) was found to be an additional predictor, along with depression and guilt, of class membership. Higher scores predicted being in the small change class ($M = 15.89$, $S.D. = 10.36$), rather than the large change class ($M = 12.24$, $S.D. = 9.96$).

Discussion

The current study adds to growing evidence that treatment outcome studies should investigate potential heterogeneity in response trajectories. The key finding was that veterans with the most severe PTSD, depression and guilt had the poorest treatment response. It

should be noted that anger and dissociation were also important variables in differentiating between classes but were not retained in the parsimonious model due to shared variance with other variables. Our findings indicate that it is the combination of PTSD, depression and guilt that is critical; the second small class with very high PTSD at intake, which showed large effect size changes, had comparable depression scores, but very low guilt scores. It may be that in cases of severe PTSD, the two co-morbidities in combination are more likely to interfere with symptom improvement than either alone. When we investigated whether other co-morbidities further predicted the differences between these two very severe classes, alcohol use was found to be an additional predictor. The combination of severe PTSD, depression and guilt, combined with alcohol use, distinguishes this low treatment response group from the other more responsive groups. Interestingly, for those with slightly less severe PTSD, depression and guilt (that is, the high-symptom/large change and high-symptom/extra-large change groups) the combination of PTSD, depression and guilt was not a barrier to symptom improvement.

The results of this study are at odds with previous findings of greater improvement in PTSD amongst those with higher pre-treatment guilt and depression compared with those with lower initial guilt and depression (Rizvi *et al.* 2009). The authors of this previous study concluded that evidence-based PTSD treatment is effective for these co-morbid symptoms. Taking into consideration the differential effects of guilt and depression on response trajectories

depending upon the severity of PTSD, the results of the current study suggest that the combination of high guilt and depression with severe PTSD does indeed impede symptom improvement more than an elevation in one of these co-morbidities alone, or slightly lower scores on the three variables (PTSD, guilt and depression). The mechanism by which this occurs is a matter of conjecture; however, it seems likely that the combination of severe PTSD, guilt and depression interferes with the individual's capacity to fully engage in trauma-focused treatment or successfully process trauma memories. It may be that the degree of affective and cognitive flexibility required to address high levels of traumatic guilt are not available to the severely depressed individual, relative to the person with less severe depression. Equally, for the person with severe depression and PTSD in the absence of severe guilt, the cognitive and emotional work required to process traumatic memories may be less complex without the presence of guilt interfering with the trauma processing. In brief, it may be that in the absence of severe depression, standard treatments can deal with the guilt and PTSD, and in the absence of severe guilt, depression does not interfere with PTSD trauma processing. What then are the implications for treatment when all three – severe PTSD, severe depression and severe guilt – are present?

Where PTSD is co-morbid with depression, PTSD treatment guidelines recommend that the two conditions are treated concurrently unless the severity of the depression precludes effective engagement in trauma-focused therapy (Australian Centre for Posttraumatic Mental Health, 2007). The complication in applying this same principle to the triad of PTSD, depression and guilt is that guilt, in particular, is likely to be integrally linked to the traumatic event, meaning it may not be possible to effectively address guilt without addressing the trauma. The question of whether guilt can be adequately addressed with standard PTSD treatments, such as prolonged exposure, or requires a different approach is the subject of current debate in the literature (e.g. Smith *et al.* 2013; Steenkamp *et al.* 2013). The finding in the current study that veterans with the combination of PTSD, guilt and depression were not responsive to standard trauma-focused treatment would seem to support the view that a different approach is required. For clients with this triad of symptoms, it may be prudent to use a trauma-focused approach that directly targets the guilt-related cognitions as a primary focus or alternatively to directly target the depression to improve the level of cognitive function required to address the combination of PTSD and guilt in treatment. To the extent that this combination of PTSD, guilt and depression is reflective of the moral injury construct receiving

increasing attention in the veteran and military literature, a targeted approach such as Adaptive Disclosure may be indicated (Litz *et al.* 2015).

Unfortunately, despite the breadth of predictors used in this analysis, we were not able to identify the factors that predicted membership of the group with the strongest outcomes (high-symptom/extra-large change). Of particular note, in light of ongoing debate about the role of compensation seeking in poor treatment response (Frueh *et al.* 2007), compensation seeking was not a significant predictor in this study. A range of variables, including personality factors, cognitive variables such as working memory, attention and executive function (Pe *et al.* 2013), and hormonal variables such as brain-derived neurotrophic factor and glucocorticoids (Felmingham *et al.* 2013; Yehuda *et al.* 2013), epigenetics (Yehuda *et al.* 2013), or trauma-type characteristics (Stein *et al.* 2012), that were not available for this study may be at play here. Future studies would benefit from including a range of measures across the psychological, neuropsychological, neurobiological, and epigenetic domains.

Limitations

Limitations in the data used for this study need to be acknowledged. Firstly, the data were collected as part of routine programme participation with no control condition. Secondly, although statistical models made use of all available data, it was not possible to account for missing data from non-completers. Thirdly, while the Australian PTSD programme standards specify the components of treatment, treatment integrity was not independently assessed by fidelity investigations, and so some level of heterogeneity in programme content and delivery must be acknowledged. Importantly however, ICCs revealed no clustering effects for programmes. Fourthly, the findings from this study are based solely on self-report scores (PCL), as opposed to changes in clinician-measured PTSD. Finally, the entropy value of 0.639, though acceptable, was lower than the 0.8, often held as a marker for very good class distinction. This indicates a degree of imprecision within the classes.

Supplementary material

The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291717001404>.

Acknowledgements

This study was supported by the Australian Department of Veterans' Affairs. The funding organisation was not involved in the design or conduct of

the study; collection, management, analysis or interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication. All authors report no financial relationships with commercial interests. AJP had full access to all the data and had final responsibility for the decision to submit for publication. No authors are declaring a conflict of interest. The authors would like to thank the staff and participating veterans from Australia's PTSD treatment programmes.

References

- Akaike H** (1973). *Information Theory and an Extension of the Maximum Likelihood Principle*. Akademiai Kiado: Budapest, Hungary.
- Australian Centre for Posttraumatic Mental Health** (2007). *Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder*. ACPMH: Melbourne, Victoria.
- Bjelland I, Dahl AA, Haug TT, Neckelmann D** (2002). The validity of the hospital anxiety and depression scale: an updated literature review. *Journal of Psychosomatic Research* **52**, 69–77.
- Blake D, Weathers F, Nagy L, Kaloupek D, Charney D, Keane T** (1995). Clinician-Administered PTSD Scale for DSM-IV (CAPS-DX). *National Center for Posttraumatic Stress Disorder, Behavioral Science Division*. Medical Center: Boston, VA, Boston, MA.
- Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA** (1996). Psychometric properties of the PTSD Checklist (PCL). *Behaviour Research and Therapy* **34**, 669–673.
- Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D** (2010). The psychiatric sequelae of traumatic injury. *American Journal of Psychiatry* **167**, 312–320.
- Creamer M, Forbes D, Biddle D, Elliott P** (2002). Inpatient *v.* day hospital treatment for chronic, combat-related posttraumatic stress disorder: a naturalistic comparison. *Journal of Nervous Mental Disease* **190**, 183–189.
- Currier JM, Holland JM, Drescher KD** (2014). Residential treatment for combat-related posttraumatic stress disorder: identifying trajectories of change and predictors of treatment response. *PLoS ONE* **9**. doi: 10.1371/journal.pone.0101741.
- Elliott P, Biddle D, Hawthorne G, Forbes D, Creamer M** (2005). Patterns of treatment response in chronic posttraumatic stress disorder: an application of latent growth mixture modeling. *Journal of Traumatic Stress* **18**, 303–311.
- Evans L, Cowlishaw S, Hopwood M** (2009). Family functioning predicts outcomes for veterans in treatment for chronic posttraumatic stress disorder. *Journal of Family Psychology* **23**, 531–539.
- Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant R** (2013). The brain-derived neurotrophic factor val66met polymorphism predicts response to exposure therapy in posttraumatic stress disorder. *Biological Psychiatry* **73**, 1059–1063.
- Feng ZD, McCulloch CE** (1996). Using bootstrap likelihood ratios in finite mixture models. *Journal of the Royal Statistical Society. Series B (Methodological)* **58**, 609–617.
- Fontana A, Rosenheck R** (1998). Effects of compensation-seeking on treatment outcomes among veterans with posttraumatic stress disorder. *The Journal of Nervous and Mental Disease* **186**, 223–230.
- Forbes D, Hawthorne G, Elliott P, McHugh T, Biddle D, Creamer M, Novaco RW** (2004). A concise measure of anger in combat-related posttraumatic stress disorder. *Journal of Traumatic Stress* **17**, 249–256.
- Frueh BC, Grubaugh AL, Elhai JD, Buckley TC** (2007). US department of veterans affairs disability policies for posttraumatic stress disorder: administrative trends and implications for treatment, rehabilitation, and research. *American Journal of Public Health* **97**, 2143–2145.
- Hunsley J, Best M, Lefebvre M, Vito D** (2001). The seven-item short form of the dyadic adjustment scale: further evidence for construct validity. *American Journal of Family Therapy* **29**, 325–335.
- Jung T, Wickrama KAS** (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychological Compass* **2**, 302–317.
- Litz BT, Lebowitz L, Gray MJ, Nash WP** (2015). *Adaptive Disclosure: A New Treatment for Military Trauma, Loss and Moral Injury*. Guilford Press: New York, NY.
- Lo Y, Mendell N, Rubin DB** (2001). Testing the number of components in a normal mixture. *Biometrika* **88**, 767–778.
- Morris SB, Deshon RP** (2002). Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychological Methods* **7**, 105–125.
- Muthén LK, Muthén BO** (2004). *Mplus*. Version 3.1 ed. Muthén & Muthén: Los Angeles, CA.
- Otis JD, Keane TM, Kerns RD, Monson C, Scioli E** (2009). The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic stress disorder. *Pain Medicine* **10**, 1300–1311.
- Pe ML, Raes F, Kuppens P** (2013). The cognitive building blocks of emotion regulation: ability to update working memory moderates the efficacy of rumination and reappraisal on emotion. *PLoS ONE* **8**, 1–12.
- Ram N, Grimm KJ** (2009). Methods and measures: growth mixture modeling: a method for identifying differences in longitudinal change among unobserved groups. *International Journal of Behavioral Development* **33**, 565–576.
- Ramaswamy V, Desarbo WS, Reibstein DJ, Robinson WT** (1993). An empirical pooling approach for estimating marketing mix elasticities with PIMS data. *Marketing Science* **12**, 103–124.
- Rizvi SL, Vogt DS, Resick PA** (2009). Cognitive and affective predictors of treatment outcome in cognitive processing therapy and prolonged exposure for posttraumatic stress disorder. *Behaviour Research and Therapy* **47**, 737–743.
- Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M** (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption. *Addiction* **88**, 791–804.

- Schumm JA, Walter KH, Chard KM** (2013). Latent class differences explain variability in PTSD symptom changes during cognitive processing therapy for veterans. *Psychological Trauma: Theory, Research, Practice, and Policy* **5**, 536–544.
- Schwarz G** (1978). Estimating the dimensions of a model. *Annals of Statistics* **6**, 461–464.
- Smith ER, Duaxa JM, Rauch AM** (2013). Perceived perpetration during traumatic events: clinical suggestions from experts in prolonged exposure therapy. *Cognitive and Behavioral Practice* **20**, 461–470.
- Stapleton JA, Taylor S, Asmundson GJ** (2006). Effects of three PTSD treatments on anger and guilt: exposure therapy, eye movement desensitization and reprocessing, and relaxation training. *Journal of Traumatic Stress* **19**, 19–28.
- Steenkamp MM, Dickstein BD, Salters-Pedneault K, Hofmann SG, Litz BT** (2012). Trajectories of PTSD symptoms following sexual assault: is resilience the modal outcome? *Journal of Traumatic Stress* **25**, 469–474.
- Steenkamp MM, Litz BT, Hoge CW, Marmar CR** (2015). Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA* **314**, 489–500.
- Steenkamp MM, Nash WP, Lebowitz L, Litz BT** (2013). How best to treat deployment-related guilt and shame: commentary on Smith, Duax, and Rauch (2013). *Cognitive and Behavioral Practice* **20**, 471–475.
- Stein NR, Mills MA, Arditte K, Mendoza C, Borah AM, Resick PA, Litz BT** (2012). A scheme for categorizing traumatic military events. *Behavior Modification* **36**, 787–807.
- Yehuda R, Daskalakis NP, Desarnaud F, Makotkine L, Lehrner AL, Koch E, Flory JD, Buxbaum JD, Meaney MJ, Bierer LM** (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Frontiers in Psychiatry* **4**, 118.
- Yehuda R, Hoge CW** (2016). The meaning of evidence-based treatments for veterans with posttraumatic stress disorder. *JAMA Psychiatry* **73**, 433–434.
- Zigmond AS, Snaith RP** (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* **67**, 361–370.