

Correspondence

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Continuing lack of evidence for the psychotic subtyping of PTSD

Gaudiano & Zimmerman¹ conclude that psychotic symptoms in post-traumatic stress disorder (PTSD) are associated with comorbid conditions, especially major depressive disorders, and that their results therefore do not support the existence of a psychotic subtype of PTSD. However, they did not evaluate certain factors that might be responsible for misinterpretation of their results. First, they did not report the severity of post-traumatic and depressive symptoms. It is possible that patients with PTSD without comorbid depressive disorder had a milder post-traumatic disorder and consequently less probability of presenting with psychotic symptoms. Second, in clinical practice the congruence of delusions and hallucinations with traumatic events seems to be distributed across a continuum: at one extreme there is complete congruence with trauma and at the other there are exuberant and bizarre symptoms similar to those described in schizophrenia. The elucidation of the possible existence of a psychotic subtype of PTSD must necessarily include the development of adequate instruments to measure severity and congruence of psychotic symptoms in ‘non-psychotic’ conditions (e.g. mood and anxiety disorders), as well as their biological correlates.

- 1 Gaudiano BA, Zimmerman M. Evaluation of evidence for the psychotic subtyping of post-traumatic stress disorder. *Br J Psychiatry* 2010; **197**: 326–7.

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doi: 10.1192/bjp.198.2.156

Authors’ reply: We welcome the response by Brietzke and colleagues to our report. First, they suggest that differences in illness severity between those with *v.* those without the comorbidities we excluded might have accounted for reductions in the prevalence rate of psychotic symptoms in our sample. To help address this point, we reanalysed our data by conducting a logistic regression of data for PTSD patients with *v.* without the excluded comorbidities as a predictor of the likelihood of having psychotic symptoms while controlling for Global Assessment of Functioning scores. Comorbid status remained a significant predictor. It is important to clarify we did not exclude all comorbidities from the PTSD sample: we removed only those that also allow for the presence of psychotic symptoms (e.g. schizophrenia, bipolar disorder). Other comorbid diagnoses

(e.g. anxiety disorders) remained in the refined PTSD sample showing the low prevalence of psychosis. Therefore, we do not believe that differences in illness severity can adequately explain our findings.

Second, Brietzke *et al* point out that psychotic symptoms in PTSD probably fall along a spectrum from congruent (e.g. hallucinations related to vivid re-experiencing of the trauma) to non-congruent (e.g. bizarre, non-trauma-related hallucinations). We agree with this observation in general, but disagree that congruence criteria are likely to clarify these issues from a diagnostic standpoint. The distinction between congruent *v.* non-congruent psychotic symptoms in primary mood disorders is known to lack prognostic value and patients frequently exhibit characteristics of both at the same time.¹

We agree with Rosen & Lilienfeld² that continued conceptual confusion regarding the PTSD diagnosis suggests the need for greater caution, rather than a rush to expand the criteria to encompass larger groups of clinical presentations, until the validity of the core features of the PTSD diagnosis can be better established. We also disagree with Breitzke *et al* that investigations of biological correlates of PTSD are likely to shed much more light on these issues. Extensive previous research in this area has found a lack of evidence for biomarkers linked specifically to the PTSD diagnosis as opposed to those that cut broadly across diagnostic categories and clinical presentations.²

- 1 Gaudiano BA, Uebelacker LA, Miller IW. Course of illness in psychotic mania: is mood congruence important? *J Nerv Ment Dis* 2007; **195**: 226–32.
- 2 Rosen GM, Lilienfeld SO. Posttraumatic stress disorder: an empirical evaluation of core assumptions. *Clin Psych Rev* 2008; **837**: 837–68.

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doi: 10.1192/bjp.198.2.156a

Is transference-focused psychotherapy really efficacious for borderline personality disorder?

In their study of treatment for borderline personality disorder, Doering *et al* state that their results ‘demonstrate the significant superiority of transference-focused psychotherapy with regard to the primary outcome criteria of drop-out rate and suicide attempts during the treatment year’ when compared with treatment by experienced community psychotherapists.¹ They report that ‘significantly fewer participants dropped out of the transference-focused psychotherapy group (38.5% *v.* 67.3%) and also significantly fewer attempted suicide ($d = 0.8$, $P = 0.009$)’.

In our view, this interpretation of primary outcome criteria might lead to misunderstandings. As regards suicidality, the authors suggest that the *P*-value of 0.009 would relate to absolute numbers of attempted suicides during the treatment year. However, the actual difference in suicide attempts during the treatment year (7/52 *v.* 11/52) is not significant ($P = 0.44$, continuity-corrected χ^2 -test, LOCF analysis). The significant *P*-value reported by the authors seems to correspond to change scores (defined as $1/0 - 1$ by the authors), not to suicide attempts during the treatment year, which seems to be the outcome as defined in the study protocol (trial NCT00714311). The authors further suggest that the effect size of 0.8 would refer to the between-group comparison. However, the reported effect size seems to correspond to the within-group comparisons reported in Table DS2. The between-group effect size for suicide attempts during the treatment year would be small.

The other primary outcome to assess efficacy was defined as the rate of participants not receiving the allocated treatment plus the rate of participants who discontinued the allocated treatment. Even when accepting that patients not even starting treatment were included in a measure of treatment efficacy, it seems problematic to ascribe differences in this criterion to the efficacy of transference-focused psychotherapy without excluding accumulative effects of alternative explanations. The higher rate of non-starters among patients randomised to community therapists (the control condition) compared with those randomised to transference-focused psychotherapy (25% *v.* 13%) and the substantially higher rate of patients stopping treatment in the control group within the first month (Fig. 2 of the paper) might reflect a general preference of participants for transference-focused psychotherapy rather than its superior efficacy. Furthermore, the authors have not mentioned that this criterion combining non-starters and 'drop-outs' as primary outcome of efficacy was introduced *post hoc* (for *post-hoc* changes in the definition of primary outcome criteria see <http://clinicaltrials.gov/archive/NCT00714311>). Without addressing this issue, the statistical implications of this proceeding are difficult to evaluate.

As for the secondary outcome measures, the picture seems to be mixed. Some of the LOCF analyses indicated lower scores after transference-focused psychotherapy (e.g. number of borderline criteria, level of personality organisation). Other scores (e.g. general psychopathology, depression) were numerically higher after transference-focused psychotherapy and did not improve significantly more under it ($P=0.92$ and $P=0.85$ for general psychopathology and depression respectively).

Recapitulating, it seems that the claimed efficacy of transference-focused psychotherapy does not follow from the primary outcome criteria. Accordingly, further research seems necessary to establish the efficacy of this therapy in the treatment of borderline personality disorder.

- 1 Doering S, Hörz S, Rentrop M, Fischer-Kern M, Schuster P, Benecke C, et al. Transference-focused psychotherapy *v.* treatment by community psychotherapists for borderline personality disorder: randomised controlled trial. *Br J Psychiatry* 2010; **196**: 389–95.

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doi: 10.1192/bjp.198.2.156b

Author's reply: Kleindienst and colleagues argue that our interpretation of the treatment outcome with regard to suicide attempts might lead to misunderstandings. They are right that a χ^2 -test comparing the absolute number of suicide attempters in both groups, transference-focused psychotherapy and treatment by experienced community psychotherapists, is not significant. However, this test does not seem appropriate in the present context, since the baseline, that is the number of suicide attempters during the year before treatment, was not equal in both groups (18 in the transference-focused psychotherapy group *v.* 12 in the community psychotherapists group). Thus, a statistical approach had to be employed that controls for baseline data. Since no χ^2 -test exists that controls for baseline values, we defined change scores that allow for baseline control within a Mann-Whitney U-test. This test generated the $P=0.009$ that, in our opinion, depicts the real changes in suicide attempters in both groups. A between-group effect size of 0.55 for the time \times group

interaction in suicide attempts was calculated from the χ^2 -statistics of the change scores ($\chi^2=7.126$, d.f.=2, $P<0.028$). Table DS2 of our paper only reports within-group effect sizes; between-group effect sizes were not calculated.

The issue of treatment drop-out is a limitation of this study, which has been thoroughly controlled for and discussed in our paper. After the decision to use treatment drop-out as a primary outcome criterion, we preferred to keep strictly to the intent-to-treat algorithm that demands every randomised patient to be part of the outcome analysis. Nevertheless, to address the understandable criticism raised by Kleindienst and colleagues, we repeated the drop-out analysis after excluding from it patients who did not begin therapy after randomisation. This analysis still revealed a significantly lower number dropping out of the transference-focused psychotherapy group (15 *v.* 23; $\chi^2=5.750$, d.f.=1, $P=0.016$).

The changes in the primary outcome criteria had been made following the impression of an ongoing discussion in the literature addressing the adequacy of DSM-IV diagnostic criteria as outcome criteria in treatment studies.^{1,2} Since our initial outcome criteria 'number of DSM-IV borderline criteria' and 'GAF score' revealed an even stronger superiority of transference-focused psychotherapy, we did not report this *post-hoc* change, because a bias in our decision was not suspected.

We thank Kleindienst and colleagues for their criticism and the Editor for giving us the opportunity to clarify important issues regarding our study. We hope that our comments will eliminate doubts concerning the fact that our study documents the efficacy of transference-focused psychotherapy for the treatment of borderline personality disorder.

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- 2 Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. *Am J Psychiatry* 2007; **164**: 929–35.

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doi: 10.1192/bjp.198.2.157

Ziprasidone and the relative risk of diabetes

Kessing *et al*¹ describe the risks of diabetes in clinical practice from a large-cohort, observational study of Danish patients requiring antipsychotics. We believe that the relative risks of subsequent incident diabetes that they report for individual antipsychotics are at odds with established literature. The preponderance of evidence has demonstrated that ziprasidone has limited effect on metabolic indices associated with the development of diabetes. We present some of that evidence below.

In the CATIE study of 1493 patients with schizophrenia receiving olanzapine, quetiapine, risperidone, ziprasidone or perphenazine for up to 18 months, ziprasidone was the only drug associated with improvement in glycosylated haemoglobin, total cholesterol and triglycerides. Meyer and colleagues² reported that, in the CATIE trial, the prevalence of metabolic syndrome increased for olanzapine (from 34.8% to 43.9%) but decreased for ziprasidone (from 37.7% to 29.9%), and that the comparison between ziprasidone and olanzapine was statistically significant ($P=0.001$).

In the EUFEST study of 498 patients with first-episode schizophrenia assigned to haloperidol, amisulpride, olanzapine,

quetiapine or ziprasidone for 12 months, weight change was greatest on olanzapine and among the lowest on ziprasidone.³ Ziprasidone was not associated with untoward effects on any other metabolic risk factors.

A pooled analysis in 2009 of over 100 Pfizer-sponsored randomised controlled trials found no significant differences between 1605 individuals given ziprasidone and 677 given placebo in total cholesterol, fasting glucose or fasting triglycerides (details available on request).

Yood *et al.*,⁴ in a 55 287-member inception cohort of antipsychotic users, found 357 cases of newly treated diabetes. Ziprasidone was among the group of agents with the lowest risk of diabetes. Patients exposed to olanzapine and clozapine had an increased risk of the illness.

A consensus statement on antipsychotic drugs and obesity published by the American Diabetes Association *et al* in 2004 concluded that increased risks of obesity, dyslipidaemia and diabetes are most associated with clozapine and olanzapine; little or no significant weight gain, diabetes and dyslipidaemia was associated with aripiprazole and ziprasidone, although it should be noted that these agents had not yet been used extensively at that time.⁵ Further, the panel suggested switching patients who develop worsening glycaemia or dyslipidaemia to a second-generation antipsychotic not associated with significant weight gain or diabetes (i.e. ziprasidone or aripiprazole). Standards of practice that promote agents with lower metabolic risks may be a confounding factor in naturalistic studies.

Kessing *et al* acknowledge that 'individuals at higher risk of diabetes because of a personal history of obesity or inactivity, a family history of diabetes or other risk factors may have been prescribed agents perceived to confer a lower risk of diabetes'. This channelling bias affects the generalisability of their results.

They report a low risk of diabetes for aripiprazole, but the drug did not become commercially available in Denmark until 2004, only 1.5 years before the end of this 10-year study. A small number of patients were exposed for a limited period of time, making the direct comparison with ziprasidone not meaningful.

With regard to Table 3, given the widely differing times of drug exposure and the ultimate position of any individual agent within a single patient's treatment regimen, conclusions about the risk of an individual agent *v.* a drug class may be inappropriate based on this study design.

We are concerned about how clinicians will interpret Kessing *et al*'s findings for ziprasidone, as the results stand in contrast to the relative risks for diabetes reported in the established literature.

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- 2 Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, et al. Change in metabolic syndrome parameters with antipsychotic treatment in

the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res* 2008; **101**: 273–86.

- 3 Kahn R, Fleischhacker WW, Karaya O, Siu C, Pappadopoulos E, EUFEST Study Group (2009) EUFEST: the effects of first and second generation antipsychotics on metabolic and cardiovascular risk factors. In *American Psychiatric Association 162nd Annual Meeting, 2009 New Research Abstracts*, Abstract NR1-043. APA, 2009.
- 4 Yood MU, DeLorenze G, Quesenberry, CP Jr, Oliveria SA, Tsai AL, Willey VJ, et al. The incidence of diabetes in atypical antipsychotic users according to agent – results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* 2009; **18**: 791–9.
- 5 American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (consensus statement). *Diabetes Care* 2004; **27**: 596–601.

Declaration of interest

D.V., D.K. and O.N.K are employed by Pfizer Inc.

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doi: 10.1192/bjp.198.2.157a

Authors' reply: We thank Dr Vanderburg and colleagues for their comments on our paper. We used observational, non-randomised, routinely collected data to describe the rate of incident diabetes among patients treated with antipsychotics in clinical practice. These data reflect the way antipsychotics are handled by individual clinicians on the basis of their knowledge of effects and side-effects for the specific patient. Findings from analyses of our data cannot be used to infer causality between individual antipsychotics and diabetes and may be at odds with findings from randomised trials and other studies aimed at testing specific hypotheses. Our results on the individual antipsychotics describe the prevalence of diabetes among patients for whom the clinician decided to prescribe a given antipsychotic.

Declaration of interest

L.V.K. has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth, Servier and Janssen-Cilag.

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doi: 10.1192/bjp.198.2.158

BJPpsych

The British Journal of Psychiatry

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BJP 2011, 198:156.

Access the most recent version at DOI: [10.1192/bjp.198.2.156](https://doi.org/10.1192/bjp.198.2.156)

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