The impact of gender on treatment effectiveness of body psychotherapy for negative symptoms of schizophrenia: A secondary analysis of the NESS trial data

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ARTICLE INFO

ABSTRACT

Despite promising findings from small-scale studies suggesting that body psychotherapy may be an effective treatment for negative symptoms, these results were not replicated in a recent multisite trial. In this trial a far smaller proportion of women were recruited relative to earlier studies, which may be an issue given the gender mix of the sample evaluated has been found to affect trial outcomes in schizophrenia. Using data from our multisite trial, the interaction between gender and treatment allocation as a predictor of outcomes was examined in 275 participants (72 women and 203 men) randomised to either a body psychotherapy or Pilates group. Negative symptoms were found to significantly reduce in women randomised to the body psychotherapy condition in comparison to Pilates, while no such effect was detected in men. Consistent with the smaller trials, this improvement was found to relate predominantly to expressive deficits. These findings suggest that body psychotherapy may be an effective treatment for negative symptoms in women. These findings emphasise the importance of sample characteristics in determining trial outcome in psychological treatment studies.

1. Introduction

Negative symptoms of schizophrenia are strongly associated to social and functional impairment (Hunter and Barry, 2012; Lysaker and Davis, 2004; Milev et al., 2005), and are unresponsive to current treatments (Fusar-Poli et al., 2015). As a result, these symptoms are considered an important unmet therapeutic need in a large proportion of cases (Kirkpatrick et al., 2006). Negative symptoms comprise of two distinct subdomains, with anhedonia, amotivation and asociality representing experiential deficits, and alogia and blunted affect representing expressive deficits (Blanchard and Cohen, 2006; Horan et al., 2011). In the 2014 NICE guidelines (NICE, 2014), creative arts therapies, such as body psychotherapy, were recommended as one effective treatment for negative symptoms. However, in a recent large-scale trial of body psychotherapy, no effects of treatment of negative symptoms were detected (Priebe et al., 2016).

The body psychotherapy NESS trial (Priebe et al., 2016) was an

advance on smaller studies by being adequately powered to detect clinically meaningful differences, including 275 participants. The trial had good internal and external validity with a high rating on the Clinical Trials Assessment Measure (88/100), designed to provide quality ratings for psychological treatment studies (Tarrier and Wykes, 2004). The therapy was fully manualised with consistently high treatment fidelity, and the treatment was compared to an active control condition to account for the non-specific effects of structured group activity. Group attendance rates in both arms compared favourably with similar creative arts therapies studies with this patient population (Crawford et al., 2012), while the study retention rate was excellent (96.7% at end of treatment).

Two other randomised controlled trials have been identified as providing data on the effects of body psychotherapy in addition to the NESS trial (Martin et al., 2016; Röhricht and Priebe, 2006). In the Röhricht and Priebe (2006) study large effect size improvements in negative symptoms were detected as compared to a supporting

counselling group, with significant improvements in blunted affect and motor retardation evident. In Martin et al. (2016) study, similar effect size improvements were detected relative to treatment-as-usual, with strong improvements found in blunted affect in particular. In NESS, while no effect on negative symptoms was detected, a significant treatment effect on expressive deficits was found, suggesting a greater degree of consistency between the study findings than a first evaluation of the primary outcomes may suggest. Given the current lack of clinically effective treatments for negative symptoms (Fusar-Poli et al., 2015), exploring why this large scale trial did not replicate the findings of the smaller studies may be important in improving recovery opportunities for at least some people with psychosis.

The reason for the differences in outcomes between these studies and the NESS trial is currently unclear. Given physical activity has been found to improve various aspects of psychological wellbeing in schizophrenia (Holley et al., 2011), it is possible that both arms of the NESS study were equally effective. However, the small within-group improvements suggest that this alone cannot account for the differences noted between the studies. A second possibility may relate to variations in the recruited samples. Many of the socio-demographic and clinical characteristics reported in the three studies were similar. One notable exception to this however is that in the full-scale trial a far lower proportion of women were recruited; in the NESS study, 24% of the sample were women, in comparison to 51% in the Röhricht study and 47% in the Martin study. This may be significant, given men have been found to experience significantly poorer premorbid and social functioning (Goldstein and Link, 1988), more pervasive neurodevelopmental abnormalities (Nopoulos et al., 1997), earlier illness onset (Häfner, 2003), are typically less emotionally expressive in response to external stimuli (Kring and Gordon, 1998), and to be more likely to experience extra-pyramidal side effects (Smith, 2010), all of which may impact treatment response in negative symptoms. However, while there is some evidence to suggest that women respond better to antipsychotic treatment (Abel et al., 2010; Usall et al., 2007), and CBT-orientated treatment for depressed patients with chronic pain (Pieh et al., 2012), we could find no studies examining the impact of gender on treatment response in group psychosocial interventions for schizophrenia. While there is some evidence to suggest that negative symptoms are both more severe and more prevalent in males (Galderisi et al., 2012; Morgan et al., 2008), a number of other studies have found no differences between the sexes (see Ochoa et al., 2012), suggesting that negative symptoms remain a significant issue for both men and women.

The primary aim of this study was to assess the moderating effects of gender on body psychotherapy as a treatment for negative symptoms using the NESS data (Priebe et al., 2016). Given the effects of body psychotherapy in the earlier studies have been found predominantly in expressive symptoms such as blunted affect (Martin et al., 2016; Röhricht and Priebe, 2006), analysis on expressive and experiential deficits were considered separately, in addition to assessing negative symptoms as a single construct. In the Röhricht study, clinical improvements were found to occur in negative symptoms only (Röhricht and Priebe, 2006), so an examination of the interaction effect between gender and treatment allocation on positive and general symptoms was completed to examine the specificity of the effect, and the consistency with earlier studies.

2. Methods

2.1. Design

The study is a secondary analysis of a blinded, parallel-arm randomised controlled trial. A full description of the design is outlined in the protocol (Priebe et al., 2013), and details of the procedures and study implementation are available in the published full report (Priebe et al., 2016). All participants were randomised, with equal probability,

to a 20-session body psychotherapy or Pilates group.

2.2. Participants

All participants were outpatients recruited from five different NHS Trusts across the UK. The inclusion criteria included an ICD-10 diagnosis of schizophrenia; a score of ≥18 on the Positive and Negative Syndrome Scale (PANSS) negative subscale (Kay et al., 1987); no change in the type of antipsychotic medication prescribed for at least 6 weeks; aged 18–65; an ability to provide informed consent; and a willingness and ability to participate in physically active groups. Prior to recruitment all participants provided informed consent.

2.3. Outcomes

In accordance with the original trial, the main outcome of interest for this investigation was the PANSS negative subscale at end of treatment (Kay et al., 1987). Expressive and experiential symptoms were examined separately using the Clinical Assessment Interview for Negative Symptoms (CAINS; Kring et al., 2013). The CAINS is a 13-item semi-structured interview designed to address the methodological and conceptual limitations of earlier negative symptom assessment tools (Blanchard et al., 2011). The experiential subscale consists of nine items, measuring how frequently they take part in social and occupational activities, their anticipation of pleasure, and their motivation to complete activities and develop or maintain relationships. The expressive subscale consists of four items, measuring deficits in vocal and gestural aspects of expression.

In order to examine the specificity of the findings, the PANSS positive and general subscales were evaluated. The Calgary scale was adopted as a measure of depression (Addington et al., 1993), EPS were measured using the Simpson Angus Scale (SAS; Simpson and Angus, 1970), and the number of social contacts participants reported over the previous week was recorded using an adapted version of the Social Network Scale (SNS; Dunn et al., 1990). The Client Service Questionnaire was included as a measure of treatment acceptability at end of treatment (CSQ; Attkisson and Zwick, 1982). Finally, the number of sessions each participant attended were assessed, recorded by the group co-facilitators after every session.

2.4. Body psychotherapy condition

The body psychotherapy treatment was a 90-min, 20-session group intervention held twice a week on non-consecutive days. The group was facilitated by an accredited dance movement psychotherapist, and assisted by a volunteer co-facilitator. The structure of the therapy is outlined in the published manual (Röhricht, 2000) and comprises of five sections. The first section is an opening circle to initiate communication between participants and draw focus towards the body. The second is a warm-up section to stimulate, promote self-awareness, and conduct reality testing exercises. The third includes structured exercises to address bodily disturbances. The fourth includes creative exercises to encourage the use of body as a source of expression and enjoyment. The fifth section is a closing circle, used to review session and disengage from the therapeutic process. In all sections, a key component of the therapy is the facilitation and development of verbal and pre-verbal communication between participants.

2.5. Physical activity group condition (Pilates)

In order to mirror the structure of the body psychotherapy intervention, the physical activities group was also a 90-min, 20-session group held twice a week on non-consecutive days, held in the same venue as each corresponding body psychotherapy group. The groups were facilitated by an accredited Pilates instructor, and assisted

by a volunteer co-facilitator. The group was structured as a beginners-level Pilates group, with a guide developed based upon the Pilates Union Matwork Manual (Newham, 2010).

2.6. Analysis plan

In the first part of the analysis, the impact of gender on treatment effectiveness for negative symptoms as a single construct was examined. A mixed-effects model, fitted by restricted maximum likelihood, was used with the PANSS negative symptom subscale at end of treatment included as the dependent variable, with fixed effects for the baseline PANSS negative subscale score, gender, treatment allocation, and the study centre (which was used in the randomisation stratification). A random effect for the therapy group was included to model for any clustering by group. To examine the impact of gender on treatment outcome, an interaction term between gender and treatment allocation was included, and assessed for significance using the Wald statistic.

As part of the analysis, a number of potential extraneous factors which may explain any effect of gender on treatment outcomes were considered. These include: baseline depression scores, given depression can induce secondary negative symptoms (Carpenter et al., 1985), can respond to body psychotherapy (Röhricht et al., 2013), and is typically more severe in women with psychosis (Goldstein and Link, 1988). Extrapyramidal symptoms (EPS), given these can mimic negative symptoms (Carpenter et al., 1985) and are more prevalent in men on antipsychotic medication (Abel et al., 2010). Number of social contacts, due to women with psychosis typically having a more developed social network (Thorup et al., 2006), which may allow for more opportunities to implement any skills learnt during treatment. Prescribed antipsychotic medication dose was also included, with the equivalence between different medications calculated using the defined daily dose (DDD; WHO, 2012). These variables were included as covariates in the model, along with group attendance rates and treatment satisfaction reported at end of treatment to control for the possibility of any effect of treatment being attributable to differences in treatment acceptability, or a dose-response effect. Due to the very high retention rate of the original trial between baseline and follow-up (96.7%), multiple imputation was not used, and the analysis was based on an available case basis following intention to treat principles.

In the second part of the analysis, expressive and experiential deficits as measured by the CAINS were evaluated in order to determine whether any effect of treatment was specific to one particular domain of negative symptoms. In addition, the PANSS positive and general symptom subscales were evaluated in order to determine the specificity of the findings, using the same model previously outlined.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the sample, stratified by gender, are presented in Table 1. Of the 275 participants recruited, 203 were men (103 randomised to body psychotherapy and 100 to Pilates) and 72 were women (37 randomised to body psychotherapy and 35 to Pilates).

3.2. Impact of gender on treatment outcomes of body psychotherapy on negative symptoms

The mean symptom levels at baseline and end of treatment, stratified by gender, are presented in Table 2. The interaction effect between gender and treatment allocation was found to be significant (Wald's statistic=4.61, *p*=0.032; adjusted difference in means: −2.18; 95% CI=−4.17 to −0.19), with women experiencing a greater reduction in negative symptoms when randomised to body psychotherapy,

Table 1
Sample characteristics, by gender.

	Men *n*=203	Women *n*=72
Centre: *n* (%)		
East & North East London	68 (33.5)	29 (40.3)
South London	50 (24.6)	14 (19.4)
Manchester	34 (16.8)	12 (16.7)
Liverpool	51 (25.1)	17 (23.6)
Age: mean (SD)	42.07 (10.72)	42.51 (10.40)
Duration of illness: median (IQR)	10 (7 – 17)	12 (7 – 20)
Number of hospitalisations: median (IQR)	3 (1–5)	3.5 (1.5–7)
Live alone: *n* (%)	146 (71.9%)	34 (47.2%)
Have at least one child: n (%)	53 (26.4%)	36 (50.7%)
PANSS total score: mean (SD)		
Negative subscale	23.34 (4.50)	22.62 (3.81)
Positive subscale	13.89 (4.90)	14.54 (5.02)
General subscale	33.41 (8.45)	35.56 (8.08)
CAINS total score: mean (SD)		
CAINS Expressive subscale	2.42 (0.63)	2.43 (0.58)
CAINS Experiential subscale	2.00 (0.89)	1.79 (1.02)
Calgary Depression Scale: mean (SD)	4.47 (4.15)	5.32 (4.89)
Antipsychotic Dose (DDD): mean (SD)	1.65 (1.28)	1.45 (0.97)

SD, standard deviation; IQR, Inter-quartile range; PANSS, Positive and Negative Syndrome Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; DDD, Defined Daily Dose.

relative to men. Men randomised to the Pilates condition reported a slightly larger reduction in negative symptoms relative to those randomised to body psychotherapy (PANSS negative symptom mean change=−1.01 and −1.95 points respectively). In contrast, women randomised to the Pilates group reported only a very small reduction in negative symptoms (mean change=−0.27 points), in comparison to a moderate reduction in those randomised to body psychotherapy (mean change=−2.55 points). In the adjusted model, after controlling for baseline depressive symptoms, EPS, number of social contacts, attendance rates, DDD, and treatment satisfaction, the interaction remained significant (Wald's statistic=7.22, *p*=0.007; adjusted difference in means=−3.21, 95% CI −5.55 to −0.87).

3.3. Impact of gender on treatment outcomes for experiential and expressive deficits

To determine whether the effect of body psychotherapy on negative symptoms in women relate to expressive or experiential deficits (or both), the analysis completed using the PANSS negative subscale was replicated using the CAINS subscales. With the CAINS experiential subscale, no interaction effect between gender and treatment allocation was detected on outcome (Wald's statistic=0.06, *p*=0.799). In the CAINS expressive subscale however a significant interaction effect on outcome between gender and treatment allocation was detected (Wald's statistic=4.03, *p*=0.045; adjusted difference in means=−0.34, 95% CI −0.68 to −0.01.). In men, a small reduction in expressive symptoms was detected in participants allocated both to the body psychotherapy and the Pilates group (mean change=−0.10 and −0.12 respectively). In women however, a small decrease in symptoms was detected in women who were randomised to the body psychotherapy group (mean change=−0.30), while a small increase was detected in those allocated to the Pilates group (mean change=0.31).

In the adjusted model controlling for baseline depressive symptoms, EPS, DDD, number of social contacts, attendance rates and treatment satisfaction, the interaction as a predictor of expressive deficits remained significant (Wald's statistic=6.59, *p*=0.010; adjusted difference in means=−0.50, 95% CI −0.88 to −0.12), while not significant for experiential deficits (Wald's statistic=0.32, *p*=0.573).

Table 2

Comparison of symptom outcomes in the body psychotherapy and Pilates at end of treatment, after controlling for covariates, by gender[a].

Variables	Men (*n*=203)				Women (*n*=72)				Adjusted difference in means, by gender (95% CI's)[b]
	Body Psychotherapy (*n*=103)		Pilates (*n*=100)		Body Psychotherapy (*n*=37)		Pilates (*n*=35)		
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of Treatment	Baseline	End of Treatment	
PANSS									
Negative	22.93 (4.37)	21.92 (5.29)	23.77 (4.62)	21.82 (4.69)	24.14 (4.07)	21.59 (5.67)	20.97 (2.71)	20.70 (4.54)	−2.18 (−4.17 to −0.19)
Positive	13.87 (5.24)	13.32 (4.97)	13.91 (4.55)	13.30 (4.29)	14.50 (4.80)	12.64 (3.88)	14.57 (5.30)	13.24 (4.20)	−0.36 (−2.15 to 1.42)
General	33.30 (8.60)	31.25 (8.01)	33.53 (8.34)	30.86 (7.44)	36.75 (7.81)	32.08 (9.11)	34.34 (8.29)	31.82 (7.44)	−1.77 (−4.66 to 1.12)
CAINS									
Expressive	1.95 (0.83)	1.85 (0.88)	2.04 (0.95)	1.92 (1.02)	2.13 (1.01)	1.79 (1.07)	1.41 (0.90)	1.72 (1.07)	−0.34 (−0.68 to −0.01)
Experiential	2.42 (0.63)	2.29 (0.65)	2.42 (0.63)	2.26 (0.63)	2.56 (0.60)	2.26 (0.62)	2.29 (0.54)	2.03 (0.66)	0.03 (−0.23 to 0.30)

Key: PANSS, Positive and Negative Syndrome Scale; CAINS, Clinical Assessment Interview for Negative Symptoms. Values represent mean scores, with standard deviations denoted in brackets (unless otherwise stated).

[a] Covariates in the model include fixed effects for baseline symptom scores and study centre, and random effects for treatment group.

[b] Negative value indicates greater symptomatic improvement in women in the body psychotherapy group.

3.4. Impact of gender on treatment outcomes for positive and general psychotic symptoms

To examine the specificity of the findings, interaction effects between gender and treatment allocation in other areas of psychopathology were examined using the PANSS positive and general symptom subscales. No significant interaction effect was detected between gender and treatment allocation in positive symptoms (Wald's statistic=0.16, *p*=0.690) or general symptoms (Wald's statistic=1.45, *p*=0.229).

4. Discussion

4.1. Main findings

Body psychotherapy was found to significantly reduce negative symptoms of schizophrenia relative to Pilates, however this effect was found only with women. Similar to earlier studies, the improvements were found only to occur in expressive, rather than experiential deficits, whilst no effect of treatment was detected in positive or general psychotic symptoms. These results were consistent after controlling for a number of possible extraneous variables, such as baseline depressive symptoms, EPS, and social network size, and not appear to be attributable to treatment acceptability or a dose-response effect.

4.2. Strengths and weaknesses

The study has a number of strengths. The analysis was completed on data from a rigorously conducted, blinded-trial with high inter-rater reliability between the assessors, good therapist fidelity to treatment, reasonable therapy group attendance rates, and excellent study retention rates. In addition, the original NESS study is by far the largest clinical trial to be conducted in the field of body psychotherapy to date. As a result, it is likely that this is the only dataset in which interaction effects could be appropriately examined. The results were consistent with earlier findings, and did not appear to be related to a number of potential extraneous factors such as depressive symptoms, EPS, the individuals social network size, treatment satisfaction, or a dose response effect.

One important caveat to these findings is the fact that this analysis should be considered only exploratory in nature. As a result, including a pre-planned sub-group analysis examining the impact of gender on treatment outcomes in any future trials on body psychotherapy for negative symptoms would be highly informative. In addition, it is important to note that in the exploratory trial (Röhricht and Priebe,

2006) the mean reduction of negative symptoms found in the body psychotherapy arm, relative to the supportive counselling group, was larger than the difference between sexes found in the current investigation. As a result, the impact of sample difference alone cannot account for the differences between the study results. Whilst far from certain, it is possible that a number of other factors may have contributed. These include the non-specific effects of physical activity from the Pilates group, greater difficulties in maintaining blinding in the clinical setting that the exploratory trial was conducted in, and a possible therapist "practice effect" (Gold et al., 2012), which may have reduced the therapist effectiveness in NESS given each therapist could only run a maximum of two groups.

Another important issue to consider is that it is currently unclear why the NESS study recruited a significantly smaller proportion of women in comparison to the earlier studies. Whilst men have a slightly higher incidence rate of psychosis (1.4:1 men to women, 58%), the prevalence of the disorder between the sexes has been found to be broadly similar (McGrath et al., 2008). As a result, the finding that the NESS study included almost three times more men than women was surprising, even after accounting for the fact that men typically experience more severe negative symptoms and so a higher proportion may have been eligible (Ring et al., 1997). The demographic details of those who refused to participate in this study were not recorded, so it is unclear whether women were more likely to reject participation, or if they were less likely to be identified as potentially eligible. However, in both cases this may have introduced a selection bias whereby only the most appropriate women were included in the study, whilst a broader range of men were included. This being the case, these findings highlight the importance of considering sample-level characteristics both at the point of analysis, and at recruitment in future clinical trials for mental health disorders.

Another important point to consider is that while the treatment was found to be significantly more effective in women, it is unclear whether a reduction of only 2.55 points on the PANSS negative subscale translates into a clinically meaningful benefit. Given the significant impact of these symptoms on functioning and the current paucity of effective treatments (Hunter and Barry, 2012; Fusar-Poli et al., 2015), it is arguable even small improvements may be viewed as important. However, it is noteworthy that this reduction is below the 3-points change used in the original trial as an indicator of a clinically significant treatment effect (Priebe et al., 2013). Lastly, it is important to note that women randomised to the body psychotherapy group reported higher negative symptoms at baseline, relative to those randomised to Pilates. As a result, it is possible that the effect may be at least in part attributable to a regression to the mean.

4.3. Comparisons to the broader literature and future work

The finding that body psychotherapy appears to be an effective treatment for negative symptoms in female participants, but not male participants, may in-part reconcile the differences in outcomes noted in the NESS trial and other recent, small-scale studies (Martin et al., 2016; Priebe et al., 2016; Röhricht and Priebe, 2006). In the Röhricht study 51% of participants were female, and significant improvements in negative symptoms and blunted affect in particular were detected in the body psychotherapy arm, as compared to supportive counselling. A similar proportion of men to women were recruited in a recent study completed by Martin and colleagues (47% women), and similar improvements in negative symptoms and blunted affect in favor of body psychotherapy over treatment-as-usual were again detected. The current investigation suggests that the high proportion of men recruited into the NESS study may have masked a treatment effect on negative symptoms which is predominantly specific to women. Consistent with the smaller studies, the improvement in women noted was found to be related specifically to expressive deficits.

Given the relatively small treatment effect and post-hoc nature of this investigation a replication of these findings in a pre-planned analysis is required. If a consistent difference in treatment response is detected between men and women, then further work understanding the possible mechanism explaining such an effect would be informative. One possible explanation could be that there is consistent evidence to suggest that men have an earlier onset of schizophrenia relative to women (Angermeyer and Kühnz, 1988; Häfner 2003), with women, on average, being 3–5 years older at first admission. In addition, women with schizophrenia have typically been found to have better social and occupational functioning (Salokangas and Stengård 1990; Shtasel et al., 1992; Usall et al., 2002), which may be attributable to the fact that a later onset allows women to achieve more stability in their occupational and social roles before becoming ill (Riecher-Rössler and Häfner, 2000; Riecher-Rössler and Rössler, 1998). As noted by Riecher-Rössler, these differences may result in different treatment goals between the sexes, resulting in different treatment approaches being necessary in order to achieve these aims. This hypothesis is supported by the socio-demographic characteristics of this sample, where women were found more likely to have children and less likely to live alone, suggesting a more developed social network and role.

4.4. Final conclusions

The findings suggest that body psychotherapy may be an effective treatment for negative symptoms of schizophrenia in women, but not men. The reasons for this difference are not fully understood and replication is required before firmer conclusions can be drawn. However, the differences in outcome may be related to functioning being more impaired in male participants, resulting in the goals of therapy being different between the sexes (Riecher-Rössler and Häfner, 2000). These findings support the idea that not all psychotherapies may be equally appropriate for everyone with a particular symptom presentation. This study also emphasises the importance of exploring sample-level characteristics in trials of psychosocial treatments, and may in part account for why results from small-scale studies are sometimes not replicated in larger clinical trials.

Conflict of interest

None.

Role of Funding Source

Acknowledgements

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