Psychiatry Research 229 (2015) 840–843

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

No evidence of a control group response in exercise randomised controlled trials in people with schizophrenia: A systematic review and meta-analysis

Brendon Stubbs [a,b,*], Simon Rosenbaum [c], Philip B Ward [c], Felipe Barreto Schuch [d,e], Davy Vancampfort [f,g]

[a] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom
[b] Health Service and Population Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London, SE5 8AF, United Kingdom
[c] School of Psychiatry, University of New South Wales, Sydney, Australia
[d] Programa de Pós-graduação em Ciências Médicas: Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
[e] Departamento de Psiquiatria, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil
[f] KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium
[g] KU Leuven Department of Neurosciences, UPC KU Leuven, Campus Kortenberg, Kortenberg, Belgium

ARTICLE INFO

Article history:
Received 20 May 2015
Received in revised form
22 July 2015
Accepted 28 July 2015
Available online 29 July 2015

Keywords:
Exercise
Schizophrenia
Placebo response
Control group response

ABSTRACT

Increased control group responses (CGR) make it more difficult to establish the effectiveness of interventions to improve symptoms in schizophrenia. We conducted a meta-analysis of CGR within randomised control trials (RCTs) comparing exercise and a control condition in people with schizophrenia. We found no evidence of a CGR for total, positive or negative symptoms. Control group responses do not negatively impact exercise RCTs that have clearly demonstrated substantial beneficial effects of exercise in this population.

1. Introduction

The comparison of active interventions with control groups that receive either placebo or treatment as usual (TAU) has been the predominant paradigm of evidence-based medicine for many years. Meta-analyses have established that placebo responses have increased in recent years and consequently drug-placebo differences have diminished over time (Agid et al., 2013), posing a challenge for the development of new medications (Leucht et al., 2013). For instance, over a 16 year period across 28 atypical antipsychotic trials, Kemp et al., (2010) found that average symptom improvement among patients in placebo groups increased by over ten points. Recently, this was replicated by Rutherford et al. (2014) who found that across 105 trials, mean change in placebo response significantly increased over time ($n=39$, $r=0.52$, $p=0.001$).

Recently, a meta-analysis (Lindheimer et al., 2015) quantified the placebo response for psychological outcomes in exercise studies in the general population, with a mean effect size of 0.20 (95% confidence interval [CI] −0.02, 0.41). Control group participants in exercise studies conducted in people with schizophrenia do not receive a conventional placebo, since many are on antipsychotic medication or receive psychotherapy. Nevertheless, understanding if there is a control group response (CGR) in exercise studies in schizophrenia is critically important. If a CGR response is evident, demonstrating the effectiveness of exercise interventions will be more challenging and arguably more so than the more publicised challenges of antipsychotic medications.

Recently, several meta-analyses have established that exercise has a beneficial impact on schizophrenia symptoms (Rosenbaum et al., 2014; Firth et al., 2015; Vancampfort et al., In press).Thus, it is important to investigate if there is a CGR response in psychiatric symptoms in exercise RCTs. We conducted the first systematic review and meta-analysis to determine if a CGR exists in exercise studies in (a) total, (b) positive and (c) negative symptoms. Secondarily, we set out to investigate predictors of changes in each of these domains.

* Corresponding author at: Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, United Kingdom. Fax: +44 1604696484.
E-mail address: brendonstubbs@hotmail.com (B. Stubbs).

http://dx.doi.org/10.1016/j.psychres.2015.07.081
0165-1781/

2. Methods

2.1. Search procedure

Two researchers (BS, DV) searched Medline, PsycARTICLES, Embase and CINAHL from database inception to May 19th, 2015. We used combinations of key words including "exercise" OR "physical activity" AND "schizophrenia" OR "psychosis" in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles. The eligibility criteria were as follows.

2.2. Participants

Only studies including adults aged at least (i.e. mean age > 18 years) with a confirmed diagnosis of schizophrenia spectrum disorder according to the Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2013) or the International Classification of Disease (ICD) (World Health Organization, 1993) were included.

2.3. Interventions

We included studies investigating the effect of any exercise intervention that contained a control group (defined below). We excluded yoga studies.

2.4. Control conditions

We included studies that had a control group receiving TAU, defined as usual-care, wait-list control conditions or non-active arms within a trial. We excluded studies that had an active control group who received any form of aerobic exercise or structured physical activity.

2.5. Outcome measure

Our primary outcome of interest was total, negative and positive symptoms measured with a recognised outcome measure such as PANSS (Kay et al., 1987) and SAPS or SANS (Andreasen, 1984a, 1984b). We evaluated pre- and post-test scores or mean difference of schizophrenia symptoms in the control groups.

2.6. Study design

We only included randomised (RCTs).

2.7. Further eligibility and exclusion criteria

No additional exclusion criteria were applied.

2.8. Study selection

After the removal of duplicates, both reviewers independently screened the titles and abstracts of all potentially eligible articles. Articles which failed to meet the inclusion criteria were excluded and any discrepancy was resolved by discussion. Full texts of all remaining articles were obtained for analysis.

2.9. Data collection and statistical analyses

Random-effects meta-analyses were conducted using Comprehensive Meta-Analysis software (Version 3, Biostat, Englewood, NJ). We investigated mean change in total, negative and positive symptoms from baseline and completion of the intervention in the control group defined as the CGR. If mean scores and Standard deviation (SD) were not available at baseline and follow up, we used the mean change and SD in the control group. We pooled data calculating Hedges' g statistic, and 95% confidence intervals (CIs) for each analysis to quantify the mean change in total, negative and positive symptoms in the control groups (i.e. CGR). We investigated potential predictors with meta-regression analyses when there were 3 or more studies including mean age of control group, percentage of males, duration of study, duration of illness, whether schizophrenia symptoms were main outcome measure, an intention to treat (ITT) analysis was included and if a sample size calculation was included. Statistical heterogeneity was assessed using the I^2 statistic (Higgins et al., 2003).

3. Results

3.1. Search results

A total of 382 records were identified and 301 titles/abstracts were screened after the removal of duplicates. Overall, 22 full texts were considered of which 14 were excluded with reasons (see Appendix 1) and 8 studies (Beebe et al., 2005; Acil et al., 2008; Pajonk et al., 2010; Behere et al., 2011; Gholipour et al., 2012; Varambally et al., 2012; Scheewe et al., 2013; Kaltsatou et al., 2014) met the eligibility criteria and were included in the meta-analysis.

3.2. Characteristics of included trials and participants

Overall, 127 participants were allocated to the control groups within the included studies. The mean duration of the control group timeframe was 20 weeks (SD 10). The mean age of participants was 36.2 years (SD 7.2), 74.3% were male (range 60–100%) and mean illness duration was 13.4 years (SD 9). All of the included studies control groups consisted of a waiting list or non-aerobic trial arms such as table top-football or occupational therapy. All included studies measured psychiatric symptoms with the PANSS, SAPS or SANS.

3.3. Meta-analysis of total symptom change in control group

Data from six studies (Beebe et al., 2005; Acil et al., 2008; Behere et al., 2011; Varambally et al., 2012; Scheewe et al., 2013; Kaltsatou et al., 2014) including 104 people with schizophrenia, demonstrated that total psychiatric symptoms did not significantly change in the control group (g=0.110, 95% CI −0.078 to 0.298, p=0.253, I^2=55%) (Fig. 1).

3.4. Meta-regression of predictors of total symptom change

The duration of control group participation (β= −0.0143, 95% CI −0.0335 to 0.0048, p=0.14), mean age (β= 0.0085, 95% CI −0.0189 to 0.0359, p=0.54), percentage of males (β= 0.0834, −1.1218 to 1.2886, p=0.89) and illness duration (β= −0.0046, 95% CI −0.0239 to 0.0147, p=0.64) and total psychiatric symptoms (β=0.0006, 95% CI −0.0058 to 0.007, p=0.85) were all not significant moderators. Moreover whether or not study had psychiatric symptoms as the main measure (β=0.3796, 95% CI 0.0791 to −0.005, p=0.07) or an intention to treat analysis was present (β=0.3017, 95% CI −0.0584 to 0.6619, p=0.10) were non-significant moderators. All moderators are summarised in the Online appendix.

3.5. Meta-analysis of positive symptom change in control group

Pooled data from six studies (Beebe et al., 2005; Acil et al., 2008; Pajonk et al., 2010; Behere et al., 2011; Scheewe et al., 2013;