*Psychological Medicine* (2015), **45**, 1613–1627. © Cambridge University Press 2014
doi:10.1017/S0033291714002712

ORIGINAL ARTICLE

# Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data

**M. Savill*, C. Banks, H. Khanom and S. Priebe**

*Unit for Social and Community Psychiatry, WHO collaborating Centre for Mental Health Service Development, Queen Mary University of London, London, UK*

**Background.** Negative symptoms are a core component of schizophrenia which can severely impact quality of life and functional outcomes. These symptoms are understood to be highly stable but this has not been tested in a meta-analysis, despite the wealth of longitudinal data available.

**Method.** A systematic review of the literature was conducted, with eligible studies pooled into a random-effects meta-analysis. Planned meta-regressions were conducted to evaluate the impact of factors known to induce secondary negative symptoms, in addition to other possible sources of heterogeneity.

**Results.** The main analysis included 89 samples from 41 studies, totalling 5944 participants. Negative symptoms were found to significantly reduce in all treatment interventions, including in placebo and treatment as usual conditions, with a medium effect size (ES) present across all study conditions (ES = 0.66, 95% confidence interval 0.56–0.77, $I^2 = 94.0\%$). In a multivariate meta-regression, only the type of scale used was found to significantly influence negative symptom change. No difference in outcome was found between studies that excluded patients with a high level of positive or depressive symptoms, compared to those that did not.

**Conclusions.** Negative symptoms were found to reduce in almost all schizophrenia outpatient samples. A reduction was found across all conditions, with effect sizes ranging from small to large depending upon the condition type. These findings challenge the convention that negative symptoms are highly stable and suggest that they may improve to a greater extent than what has previously been assumed.

*Received 29 July 2014; Revised 20 October 2014; Accepted 22 October 2014; First published online 26 November 2014*

**Key words:** Longitudinal course, negative symptoms, schizophrenia, symptom assessment.

## Introduction

Since Bleuler coined the term schizophrenia in the early 1900s negative symptoms have been recognized as a core feature of the disorder (Bleuler, 1950). The symptoms include alogia, asociality, blunted affect, anhedonia and amotivation (Blanchard *et al.* 2011), and have been found to severely impact both quality of life and social functioning (Norman *et al.* 2000).

Historically, negative symptoms were believed to increase over time as patients experience a progressive deterioration in functioning (Kraepelin, 1971). However, in observational studies which evaluated the progressive course of these symptoms the evidence initially suggested that these are largely stable over time (Pogue-Geile & Harrow, 1985; Fenton & McGlashan, 1991; Dollfus & Petit, 1995; Eaton *et al.* 1995). Later work recognized that the course was highly heterogenous, with some negative symptoms improving, often in tandem with improvement in positive symptoms (Addington & Addington, 1991). In an attempt to explain this heterogeneity Carpenter and colleagues proposed a distinction between those attributable to factors such as hospitalization, medication side-effects, depression, and elevated positive symptoms (known as secondary negative symptoms), from primary symptoms which were regarded as a core feature of the disorder itself (Carpenter *et al.* 1985). While secondary symptoms tend to improve relatively quickly once the causes are addressed, primary negative symptoms are thought to be largely persistent (Möller, 2007).

Broadly defined, primary negative symptoms refer to negative symptoms which are present both within and during periods of positive symptom exacerbation. However, distinguishing between primary and secondary negative symptoms can be a complex undertaking given the challenges in obtaining sufficient historical information and the level of clinical expertise required by the assessors. In light of this, Buchanan

* Address for correspondence: Mr M. Savill, Unit for Social and Community Psychiatry, WHO collaborating Centre for Mental Health Service Development, Queen Mary University of London, Newham Centre for Mental Health, London E13 8SP, UK.
(Email: m.savill@qmul.ac.uk)

(2007) suggested the alternative, broader distinction of 'persistent negative symptoms', which include negative symptoms which remain present after usual treatments for secondary negative symptoms have failed. In the consensus statement for negative symptoms, it was proposed that distinguishing between primary and secondary negative symptoms was not essential for the purposes of testing therapeutics, as long as studies select participants with persistent symptoms and control for secondary sources of negative symptoms (Kirkpatrick *et al.* 2006).

To date, any advances in the treatment of schizophrenia have been found to provide only limited benefit to negative symptoms. In a meta-analysis which examined the efficacy of different second-generation antipsychotics, most were found not to provide a significant benefit over and above first-generation drugs, and in those that did the effect sizes were small (Leucht *et al.* 2009). Meta-analyses into the efficacy of adjunctive medications such as $\alpha_2$ receptor antagonists (Hecht & Landy, 2012) and glutamatergic compounds (Tuominen *et al.* 2005) show some promise, while there is some evidence to suggest that adjunctive antidepressant medication may have some limited benefit (Singh *et al.* 2010). In a broader review evaluating the different pharmacological approaches in treating negative symptoms (Arango *et al.* 2013), new drugs that act on the NMDA and $\alpha_7$ nicotinic receptors are highlighted as promising, but again more research is needed. In a series of meta-analyses on psychotherapeutic interventions, CBT was reported to have a small effect (Jauhar *et al.* 2014), social skills training a moderate effect (Kurtz & Mueser, 2008), while no effect was found for social cognitive training (Kurtz & Richardson, 2012). In a meta-analysis of cognitive remediation therapy which evaluated symptoms overall, a small effect was detected (Wykes *et al.* 2011). In the UK, NICE have previously recommended Arts therapies (NCCMH, 2010); however, this has since been challenged by the non-significant result of the MATISSE trial (Crawford *et al.* 2012). Overall, a lack of treatment efficacy has led to negative symptoms to be recognized as an unmet therapeutic need, and an important target for new interventions (Kirkpatrick *et al.* 2006).

Given the current focus on developing new interventions for negative symptoms, understanding their longitudinal course is important for future study design. Many of the earlier observational studies included inpatients, which is problematic given this population would typically receive far higher doses of antipsychotic medication and experience higher positive symptoms (Kasckow *et al.* 2001), and may reside in an under-stimulating environment (Oshima *et al*. 2003), which may induce negative symptoms secondary to the disorder itself. In addition, a number of the earlier studies included other illnesses such as schizoaffective disorder, which follows a different longitudinal course and can have poorer diagnostic stability, which again may influence symptom change over time (Malhi *et al.* 2008).

The objective of this study was to examine how negative symptoms change over time in schizophrenia outpatients, while exploring the impact of factors known to induce secondary negative symptoms. By pooling a wide variety of studies by way of meta-analysis, the aim was uncover broader trends in how these symptoms may change, as opposed to attempting to identify an estimate of effect size for a particular type of treatment. Following a systematic search, we conducted a meta-analysis of the within-group mean changes in negative symptoms. Only samples comprising exclusively of schizophrenia patients from the first assessment point were considered. Due to the expected heterogeneity between different interventions, separate effect size estimates were calculated for each treatment type. Finally, a series of planned meta-regressions were conducted to explore any impact of factors which may lead to secondary negative symptoms (Carpenter *et al.* 1985), and possible sources of methodological bias.

## Method

### *Research in context*

The systematic review was conducted following PRISMA statement guidelines (Liberati *et al.* 2009). An electronic search using the Medline, PsycINFO, EMBASE and CENTRAL databases was conducted dating back to 1962, which was when the Brief Psychiatric Rating Scale (BPRS) was first published (Overall & Gorham, 1962). The search was conducted on 26 April 2014 and contained three parameters. The first related to diagnosis, the second to negative symptoms, and the third an indicator that the study took place over at least two time points.

A hand-search of the *American Journal of Psychiatry, Acta Scandinavica Psychiatrica, British Journal of Psychiatry, Schizophrenia Bulletin, JAMA Psychiatry, The Lancet*, and *Schizophrenia Research* was conducted, either from 1962 or the date of first issue, and reference lists from all selected papers were hand-searched. During extraction, all assessments of negative symptoms, study inclusion/exclusion criteria, demographic details, industry sponsorship, and study methodology details were recorded. When necessary, corresponding authors were contacted for further information. In the case of missing standard deviations, a mean from the existing sample was imputed when possible. M.S.

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

conducted the abstract screening, 20% of which was duplicated by C.B. with minimal discrepancies in selection detected. In the full paper screening phase M.S. conducted 100% of the screening, duplicated by H.K. and C.B. screening 50% of the sample each. All discrepancies were resolved without the need for S.P. to adjudicate as planned. At the full screening phase, all data were independently extracted onto a piloted extraction sheet.

### *Eligibility criteria*

During the screening phase studies were excluded if they were clearly not relevant, did not have repeated assessments of negative symptoms at set time points, included no usable data on an exclusively schizophrenic sample, children or older adults, or were either under 10 weeks in length or over 3 years in length from the first follow-up assessment. Studies which included inpatients were considered, as long as the study included one time-point where the sample was exclusively outpatients, and then followed up from a standardized time-point from this assessment. Symptoms were required to be measured on a validated scale. Qualitative studies, case reports, letters to the editor, conference abstracts and book chapters were excluded. All articles were required to be published in a language which used Latin-based characters. Due to the analytical strategy adopted and the risk of small samples leading to biased estimates (Morris, 2000), studies with fewer than 50 participants were excluded.

### *Analysis plan*

In the pooled analysis, the measure of effect size for each study was calculated using the standardized mean change (SMC) (Becker, 1988; Morris, 2000). The estimation of the variance was calculated using the large-sample approximation method recommended by Becker (1988), which can provide accurate estimates provided the sample sizes are adequately sized (Morris, 2000). The estimate of the correlation between the baseline and end of study scores was set at 0.633, based upon datasets held at our research group (Priebe *et al.* 2007) and a subsequent sensitivity analysis.

In deciding the appropriate effects model to adopt, the decision was complicated by the likelihood that multiple arms of the same study would be separately eligible for inclusion. One method of addressing this which was recognized in the *Cochrane Handbook* (Higgins & Green, 2011), is to conduct a two-level, fixed-effects meta-analysis across arms within studies, followed by a random-effects meta-analysis across studies, as a way to account for the mix in fixed and random effects that are likely to be present. However, this model adds considerable complexity to the analysis, while the handbook itself acknowledges that 'in practice the difference between different analyses is likely to be trivial' (section 16.5.5). This being the case, the method was not used, and the DerSimonion and Laird random-effects model was adopted (DerSimonian & Laird, 1986). All analysis was completed using Stata version 11 (StataCorp, 2009).

In cases where multiple scales were used to measure negative symptoms, the primary outcome measure was selected. When negative symptoms were measured over more than two time points, only the baseline and the study endpoint data were selected.

In the first stage of the analysis samples were grouped according to whether the intervention involved testing second-generation antipsychotics, first-generation antipsychotics, adjunctive medications, non-drug interventions, or placebo/treatment as usual (TAU) arms. In the next stage a series of planned univariate meta-regressions were conducted, with those found to approach significance ($p < 0.10$) entered into a multivariate model. First, we examined the impact of length of treatment in order to assess whether there was any trend over time. Next, we tested whether there was any difference between studies which incorporated a maximum threshold for positive and depressive symptoms, compared to those that did not, in order to assess whether the degree of change in negative symptoms varied dependent upon how studies dealt with factors which can cause secondary negative symptoms. We also tested the impact of blinding the assessors, a minimum negative symptom inclusion criterion, and whether the study received industry sponsorship.

In any examination of the change in a continuous variable over time which only includes two time points the issue of regression to the mean should be considered (Chiolero *et al.* 2013). This being the case, the mean negative symptoms at baseline were added to the final multivariate model to determine the degree of additional variance that may be explained by a greater reduction in negative symptoms being caused by a higher baseline symptom levels.

## Results

A flow diagram depicting the search strategy for studies is included in Fig. 1. Of the 9480 articles screened, 49 articles were found and 41 were included in the final analysis (see Table 1). From these, a total of 89 separate samples were obtained. Of the 41 studies, five came from the USA; four each from Canada, Germany and the UK; three each from India, Spain and Turkey; two each from China, France and Italy;

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

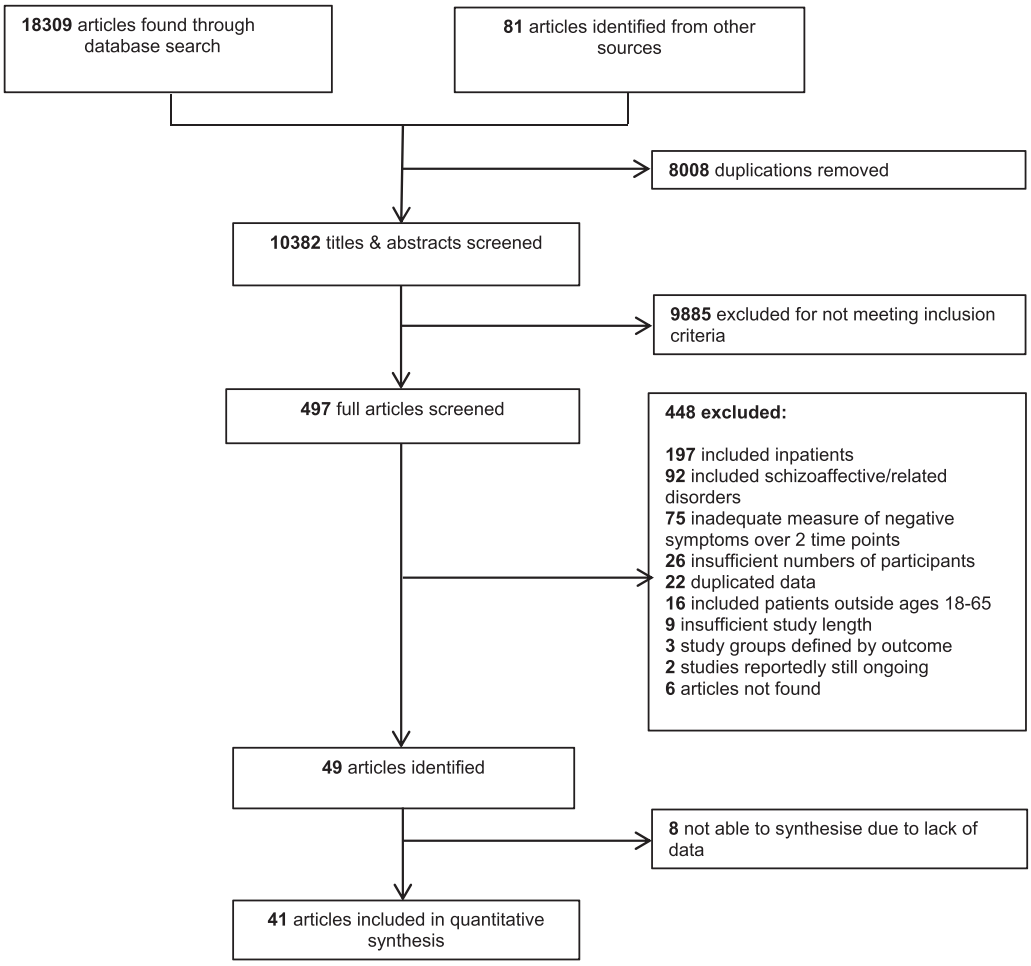


**Fig. 1.** Flow diagram outlining study selection procedure.

and one each from Brazil, Finland, Israel, Nepal, Poland and Serbia. Four studies were conducted in multiple countries, with sites in Northern America, Europe and Asia. Based on 51 samples, the median of study mean illness duration was 12.4 years (range 0.6–27.5 years). Twenty-three studies measured negative symptoms using the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987), 14 used the Scale to Assess Negative Symptoms (SANS; Andreasen, 1983), and four used the BPRS (Overall & Gorham, 1962). While studies which used alternative scales were screened, none met eligibility criteria. After pooling all 89 samples, a final total of 5944 participants were included in the meta-analysis.

As indicated in the forest plot (see Fig. 2), in all five intervention types a significant reduction in negative symptoms was found between the baseline and the follow-up assessment stage. Large effect sizes (ES) were detected in second-generation antipsychotics [ES = 1.09, 95% confidence interval (CI) 0.86–1.32, $I^2$ = 95.5%] and the adjunctive medication (ES = 0.97, 95% CI 0.68–1.26, $I^2$ = 91.7%) arms, while a small effect size was noted in the placebo/TAU group (ES = 0.33, 95% CI 0.17–0.49, $I^2$ = 91.8%).

Next, a series of meta-regressions were conducted. In the univariate analyses the scale used, intervention type, study duration, and a minimum negative symptoms inclusion criterion were all associated with negative symptom change heterogeneity (see Table 2). A maximum level of positive symptoms and previous non-response to treatment as exclusion criteria were found to approach significance ($p < 0.10$), while other variables were non-significant. In the multivariate model, only the type of scale used and the type of intervention received remained significant. Studies which used the SANS found a significantly greater reduction in negative symptoms relative to those that used the PANSS (SANS: ES = 1.02, 95% CI 0.77–1.28; PANSS: ES = 0.66, 95% CI 0.56–0.77). Collectively, the scale used and the intervention type accounted for 43.65% of the variance. In a sensitivity analysis, the sample-level baseline negative symptoms were added to the model which was found to be a significant predictor ($B$ = 0.01, S.E. = 0.00, 95% CI 0.00–0.02). However,

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

**Table 1.** *Characteristics of eligible studies*

| Authors | Year | Country | Study duration (weeks) | Outcome measure[a] | Individual symptoms reported | Intervention type[b] | *n* |
|---|---|---|---|---|---|---|---|
| Addington & Addington (2000) | 2000 | Canada | 130 | PANSS | No | TAU | 65 |
| Aguglia *et al.* (2002) | 2007 | Italy | 52 | SANS | Yes | Non-drug intervention: psychoeducation | 69 |
| | | | | | | TAU | 66 |
| Alptekin *et al.* (2005) | 2005 | Turkey | 52 | BPRS | No | TAU | 382 |
| Alvarez *et al.* (2006) | 2006 | Spain | 48 | SANS | Yes | SGA: olanzapine | 120 |
| | | | | | | SGA: risperidone | 115 |
| Amell & Llandrich (2008) | 2008 | Spain | 46 | PANSS | Yes | Non-drug intervention: skills training group | 35 |
| | | | | | | TAU | 22 |
| Bales *et al.* (2009) | 2009 | Nepal | 18 | PANSS | No | TAU | 30 |
| | | | | | | TAU + betel nuts | 30 |
| Behere *et al.* (2011) | 2011 | India | 16 | PANSS | No | Non-drug intervention: yoga group | 34 |
| | | | | | | Non-drug intervention: exercise group | 31 |
| | | | | | | TAU | 26 |
| Bhowmick *et al.* (2010) | 2010 | India | 12 | SANS | No | SGA: amisulpride | 40 |
| | | | | | | SGA: olanzapine | 40 |
| Bio & Gattaz (2011) | 2011 | Brazil | 26 | PANSS | No | TAU | 57 |
| Bobes *et al.* (2009) | 2009 | Spain | 34 | BPRS | No | SGA: risperidone | 362 |
| Bodkin *et al.* (2005) | 2005 | USA | 12 | SANS | Yes | Adjunctive: selegiline | 33 |
| | | | | | | Placebo | 34 |
| Crawford *et al.* (2012) | 2012 | UK | 52 | PANSS | No | TAU | 137 |
| | | | | | | Non-drug intervention: activity group | 140 |
| | | | | | | Non-drug intervention: art therapy group | 140 |
| Fleischhacker *et al.* (2003) | 2003 | Multi | 52 | PANSS | No | SGA: risperidone | 120 |
| | | | | | | SGA: risperidone | 228 |
| | | | | | | SGA: risperidone | 267 |
| Gaebel *et al.* (2007) | 2007 | Germany | 52 | PANSS | No | SGA: risperidone | 77 |
| | | | | | | FGA: haloperidol | 74 |
| Gorna *et al.* (2008) | 2008 | Poland | 52 | PANSS | No | TAU | 88 |
| Hirsch *et al.* (2002) | 2002 | Germany | 28 | PANSS | No | SGA: ziprasidone | 110 |
| | | | | | | FGA: haloperidol | 117 |
| Kane *et al.* (2011) | 2011 | USA | 26 | PANSS | No | TAU: remained on same drug | 194 |
| | | | | | | Placebo: switched to placebo | 192 |
| Kane *et al.* (2012) | 2012 | USA | 24 | PANSS | No | Adjunctive: armodafinil | 70 |
| | | | | | | Adjunctive: armodafinil | 69 |
| | | | | | | Adjunctive: armodafinil | 71 |
| | | | | | | Placebo | 70 |
| Kaphzan *et al.* (2014) | 2014 | Israel | 12 | PANSS | No | Placebo | 22 |
| | | | | | | Adjunctive: entacapone | 23 |
| Klingberg *et al.* (2011) | 2011 | Germany | 52 | PANSS | Yes | Non-drug intervention: CBT | 99 |
| | | | | | | Non-drug intervention: CRT | 99 |
| Lasser *et al.* (2013) | 2013 | USA | 10 | SANS | No | Adjunctive: lisdexamfetamine dimesylate | 92 |
| Lecrubier *et al.* (2006) | 2006 | France | 26 | SANS | No | Placebo | 34 |
| | | | | | | SGA: olanzapine | 70 |
| | | | | | | SGA: olanzapine | 70 |

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

**Table 1** (*cont.*)

| Authors | Year | Country | Study duration (weeks) | Outcome measure[a] | Individual symptoms reported | Intervention type[b] | *n* |
|---|---|---|---|---|---|---|---|
| | | | | | | SGA: amisulpride | 70 |
| Liu *et al.* (2014) | 2014 | China | 16 | PANSS | No | Placebo | 40 |
| | | | | | | Adjunctive: minocycline | 39 |
| Loebel *et al.* (2007) | 2007 | India | 64 | PANSS | No | SGA: ziprasidone | 32 |
| | | | | | | SGA: ziprasidone | 30 |
| Loo *et al.* (1997) | 1997 | France | 26 | SANS | Yes | Placebo | 72 |
| | | | | | | SGA: amisulpride | 69 |
| Meltzer *et al.* (2010) | 2010 | USA | 52 | BPRS | No | SGA: clozapine | 40 |
| | | | | | | FGA: various first-generation drugs | 45 |
| Olie *et al.* (2006) | 2006 | Multi | 12 | PANSS | No | SGA: ziprasidone | 59 |
| | | | | | | SGA: amisulpride | 63 |
| Pach *et al.* (1998) | 1998 | Germany | 52 | SANS | Yes | FGA: flupenthixol decanoate | 63 |
| Peet & Horrobin (2002) | 2002 | UK | 12 | PANSS | No | Placebo | 31 |
| | | | | | | Adjunctive: eicosapentaenoic acid | 32 |
| | | | | | | Adjunctive: eicosapentaenoic acid | 32 |
| | | | | | | Adjunctive: eicosapentaenoic acid | 27 |
| Purdon *et al.* (2000) | 2000 | Canada | 54 | PANSS | No | SGA: olanzapine | 21 |
| | | | | | | FGA: haloperidol | 23 |
| | | | | | | SGA: risperidone | 21 |
| Ravanic *et al.* (2009) | 2009 | Serbia | 52 | PANSS | No | FGA: haloperidol | 70 |
| | | | | | | FGA: haloperidol | 35 |
| | | | | | | FGA: chlorpromazine | 65 |
| | | | | | | FGA: chlorpromazine | 40 |
| | | | | | | SGA: clozapine | 65 |
| | | | | | | SGA: clozapine | 50 |
| Richardson *et al.* (2007) | 2007 | UK | 38 | SANS | No | TAU | 46 |
| | | | | | | Non-drug intervention: art therapy group | 43 |
| Semiz *et al.* (2007) | 2007 | Turkey | 12 | SANS | No | SGA: clozapine | 97 |
| Schoemaker *et al.* (2014) | 2014 | Multi | 12 | SANS | Yes | Adjunctive: Org25935 low dose | 71 |
| | | | | | | Adjunctive: Org25935 high dose | 73 |
| | | | | | | Placebo | 70 |
| Sumiyoshi *et al.* (2007) | 2007 | USA | 26 | BPRS | No | Adjunctive: buspirone | 30 |
| | | | | | | TAU | 29 |
| Taiminen *et al.* (1997) | 1997 | Finland | 12 | PANSS | No | TAU | 39 |
| | | | | | | Adjunctive: citalopram | 36 |
| Turkington *et al.* (2008) | 2008 | UK | 78 | SANS | No | Non-drug intervention: CBT | 46 |
| | | | | | | Non-drug intervention: befriending | 44 |
| Ucok *et al.* (2011) | 2011 | Turkey | 52 | SANS | No | TAU | 52 |
| | | | | | | TAU | 41 |
| Voruganti *et al.* (2007) | 2007 | Canada | 52 | PANSS | No | SGA: olanzapine | 42 |
| | | | | | | SGA: quetiapine | 43 |

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

**Table 1** (*cont.*)

| Authors | Year | Country | Study duration (weeks) | Outcome measure[a] | Individual symptoms reported | Intervention type[b] | *n* |
|---|---|---|---|---|---|---|---|
| Xiang *et al.* (2006) | 2006 | China | 34 | PANSS | No | Non-drug intervention: community re-entry | 48 |
| | | | | | | Non-drug intervention: counselling | 48 |
| Zoccali *et al.* (2007) | 2007 | Italy | 24 | SANS | Yes | Adjunctive: lamotrigine | 26 |
| | | | | | | Placebo | 25 |
| List of studies not included in the main analysis due to insufficient data | | | | | | | |
| Adams *et al.* (2013) | 2013 | Multi | 24 | NSA-16 | No | SGA: multiple types | 130 |
| | | | | | | SGA: LY2140023 | 131 |
| Chouinard *et al.* (1975) | 1975 | Canada | 12 | BPRS | No | Placebo | 24 |
| | | | | | | FGA: amitriptyline hydrochloride | 24 |
| | | | | | | FGA: perphenazine | 24 |
| | | | | | | FGA: amitriptyline perphenazine | 24 |
| Goff *et al.* (2005) | 2005 | USA | 26 | SANS | Yes | Adjunctive: D-cycloserine | 26 |
| | | | | | | Placebo | 25 |
| Hayes *et al.* (1995) | 1995 | Australia | 44 | SANS | No | Non-drug intervention: skills training group | n/s |
| | | | | | | Non-drug intervention: discussion group | n/s |
| Liberman *et al.* (1998) | 1988 | USA | 156 | BPRS | No | Non-drug intervention: occupational therapy | n/s |
| | | | | | | Non-drug intervention: skills training group | n/s |
| Lieberman *et al.* (2013) | 2013 | Multi | 12 | SANS | No | Adjunctive: TC-5619 | 94 |
| | | | | | | Placebo | 91 |
| Marder *et al.* (2003) | 2003 | USA | 104 | SANS | Yes | SGA: risperidone + skills training | 33 |
| | | | | | | FGA: haloperidol + skills training | 30 |
| Pinto *et al.* (1979) | 1979 | UK | 78 | BPRS | No | FGA: flupenthixol decanoate | 34 |
| | | | | | | FGA: fluphenazine decanoate | 30 |

[a] PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale to Assess Negative Symptoms; NSA-16, Negative Symptom Assessment – 16.

[b] TAU, treatment as usual; SGA, second-generation antipsychotic; Adjunctive, adjunctive medication in addition to antipsychotic medication received; FGA, First-generation antipsychotic; CBT, cognitive behaviour therapy; CRT, cognitive remediation therapy.

the additional variance explained was relatively small (4.10%).

Although many of the studies evaluated extra-pyramidal symptoms (EPS) as part of their analysis (53.7%), only three studies specified an EPS maximum threshold as an exclusion criterion (Klingberg *et al.* 2011; Lasser *et al.* 2013; Schoemaker *et al.* 2014). Given the lack of data, this was not included in the meta-regression analysis. Of those studies that did report EPS, they were generally considered to be in the low range at study intake, suggesting that the impact of EPS on negative symptoms was likely to be minimal.

Given the finding that second-generation antipsychotics and adjunctive medication arms resulted in much larger effect sizes than other treatment types, contrary to our expectations based on the existing literature (i.e. Leucht *et al.* 2009; Arango *et al.* 2013), the TAU and placebo control arms that they were compared to were explored in more depth. A substantially larger effect size was detected in TAU/placebo control arms which were part of the drugs trials, in

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

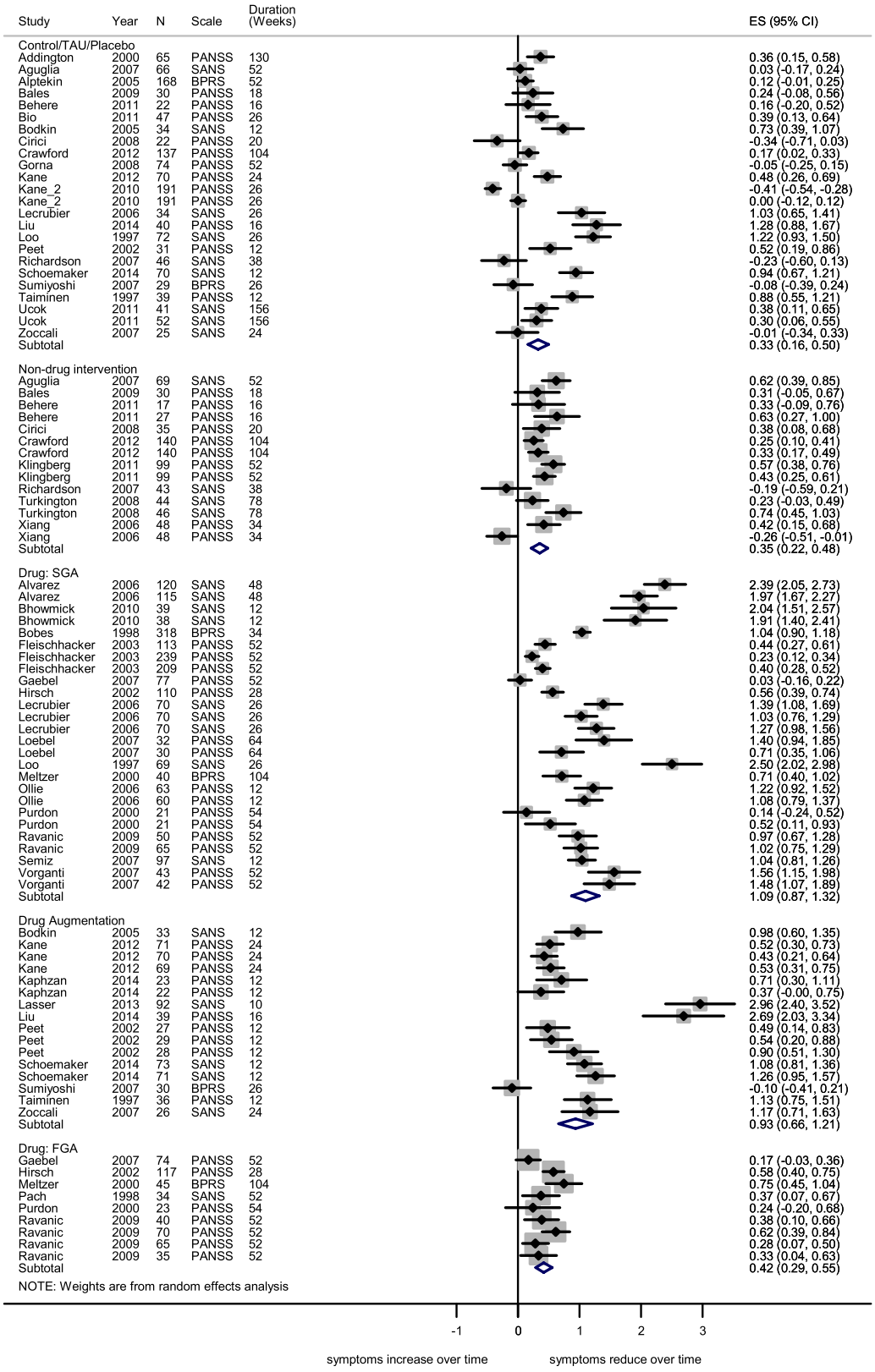


**Fig. 2.** Forest plot of the change in negative symptoms, by intervention type.

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

**Table 2.** *Univariate and multivariate meta-regressions examining the heterogeneity of negative symptom change*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Predictor of negative symptom change | Coefficient | 95% CI | *p* | Coefficient | 95% CI | *p* |
| Study duration | −0.01 (0.00) | −0.01 to −0.00 | 0.035 | −0.00 (0.00) | −0.01 to 0.00 | 0.388 |
| Scale used (compared to PANSS) | | | 0.002 | | | |
| SANS | 0.49 (0.14) | 0.21 to 0.77 | | 0.43 (0.13) | 0.16 to 0.70 | 0.002 |
| BPRS | −0.12 (0.26) | −0.63 to 0.40 | | −0.07 (0.23) | −0.54 to 0.39 | 0.760 |
| Intervention type (compared to SGA) | | | <0.001 | | | |
| Non-drug intervention | −0.75 (0.18) | −1.11 to −0.38 | | −0.67 (0.18) | −1.04 to −0.30 | 0.001 |
| TAU/placebo | −0.76 (0.16) | −1.07 to −0.45 | | −0.72 (0.16) | −1.04 to −0.40 | <0.001 |
| Drug: FGA | −0.68 (0.18) | −1.10 to −0.25 | | −0.53 (0.20) | −0.93 to −0.13 | 0.010 |
| Drug: augmentation | −0.12 (0.18) | −0.48 to 0.23 | | −0.17 (0.18) | −0.54 to 0.19 | 0.336 |
| Min negative symptoms | 0.37 (0.13) | 0.10 to 0.63 | 0.007 | 0.11 (0.12) | −0.13 to 0.36 | 0.356 |
| Max positive symptoms | 0.26 (0.14) | −0.02 to 0.54 | 0.071 | 0.05 (0.13) | −0.21 to 0.32 | 0.685 |
| Study supported by industry sponsorship | 0.15 (0.14) | −0.14 to 0.43 | 0.309 | | | |
| Exclusion: previous non-response | 0.42 (0.18) | 0.07 to 0.78 | 0.019 | 0.05 (0.17) | −0.29 to 0.40 | 0.752 |
| Raters blinded to allocation[a] | −0.18 (0.15) | −0.47 to 0.12 | 0.234 | | | |
| Exclusion: moderate levels of depression | 0.13 (0.17) | −0.21 to 0.46 | 0.452 | | | |

CI, Confidence interval; PANSS, Positive and Negative Syndrome Scale; SANS, Scale to Assess Negative Symptoms; BPRS, Brief Psychiatric Rating Scale; SGA, second-generation antipsychotic; TAU, treatment as usual; FGA, first-generation antipsychotic.

Values within parentheses are standard errors.

[a] One study not included due to lack of data.

comparison to those that were not (ES = 0.67, 95% CI 0.41–0.93, in comparison to ES = 0.15, 95% CI 0.04–0.25). In a subsequent meta-regression this difference was found not to be attributable to either higher negative symptoms at baseline, or the type of assessment tool used, which were significant predictors in the full model.

### *Examination of individual negative symptoms*

In 18 samples over nine studies the change in individual negative symptoms were also reported (see Table 1). Seven studies used the SANS as the rating tool, while two used the PANSS. Scores from different scales were combined using the method proposed by Lyne and colleagues (2012). A significant reduction was found in all four of the symptoms measured (affective blunting, alogia, avolition-apathy, anhedonia-asociality). Of the four, alogia appeared to reduce the least (ES = 0.64, 95% CI 0.45–0.83) and avolition-apathy the most (ES = 0.77, 95% CI 0.53–1.01); however, the difference between the items appeared minimal.

### *Eligible studies not pooled into the main analysis*

Eight studies were found to be eligible, but could not be included in the main analysis (see Table 1). In line with the main results, 11 samples found some form of reduction in negative symptoms from baseline to end of study, five saw no change, and in two the change was not specified.

## Discussion

### *Main results*

The meta-analysis provided a clear result; negative symptoms of schizophrenia tend to improve significantly in an outpatient setting. A reduction in negative symptoms found across all intervention types, with the effect sizes ranging from small to large. A significant reduction was found in all four of the separate negative symptoms examined, covering both experiential and expressive features of the disorder. While substantial heterogeneity was present in the sample, a series of planned meta-regressions indicated that there was no difference in the reduction between studies which did and did not exclude participants with higher levels of positive or depressive symptoms. In addition, study-level methodological differences such as whether assessors were blinded, the symptom eligibility criteria, or whether the study received industry sponsorship did also not appear to influence the result.

### *Strengths and limitations*

One of the main strengths of the study is that, despite the broad range of study interventions considered, the

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

findings are consistent. Of the 89 study arms included, only one found a clear significant increase in symptoms. In this case, the sample was part of a continuation study where patients who had previously responded well to their SGA medication were then switched to a placebo (Kane *et al.* 2011). In addition, when testing for the effect of regression to the mean, adding baseline negative symptoms to the multivariate model appeared to add relatively little additional explanatory power of the variance (4.1%), suggesting the findings are relatively robust. A further strength of this study is that despite the broad study inclusion criteria, removing samples which included inpatients at baseline, and other psychotic diagnoses, meant the participant inclusion criteria were relatively stringent in comparison to other observational studies that have looked at how negative symptoms change over time (i.e. Pogue-Geile & Harrow, 1985; Fenton & McGlashan, 1991; Dollfus & Petit, 1995; Eaton *et al.* 1995). When testing for heterogeneity, no difference in the effect size was detected between studies which excluded participants with elevated positive and depressive symptoms, which suggests the change unlikely to be attributable to a reduction in these factors which can induce secondary negative symptoms.

One limitation of the study is that because of the variance estimation method adopted a number of studies were excluded due being too small. However, given there is evidence to suggest that smaller studies can often present larger effect sizes (i.e. Zhang *et al.* 2013), our findings may have led to a more conservative estimate of the effect size. Another limitation is that, despite the number of studies included in the analysis ($n = 41$), the final sample of 5944 patients was smaller than what was anticipated. This was due to a number of the larger studies either containing inpatients (Lieberman *et al.* 2005), not using a validated negative symptoms scale (Dossenbach *et al.* 2004), or including patients with other psychotic disorders.

Another important issue to consider is that it is difficult to assess to what extent the reduction in severity is attributable to improvements in primary or secondary negative symptoms. However, difficulties making this distinction in research trials is not new (Buchanan, 2007), and the consensus statement suggests that such a distinction is not essential in trials as long as the symptoms are persistent and causes of secondary negative symptoms are adequately controlled for (Kirkpatrick *et al.* 2006). In this analysis, the eligible studies typically reported participants as being highly chronic in nature, reflected in the large median duration of illness (12.4 years), and many defined their sample as treatment-resistant, stable, non-acute, or in a maintenance period. Regarding whether secondary negative symptoms can be adequately controlled for using study-level inclusion/exclusion criteria in a meta-regression of the heterogeneity present in a meta-analysis, this is also up for debate. However, despite these issues the high consistency of the directional change in negative symptoms in an outpatient sample, and the fact that there was no difference in this change between studies which did and did not control for factors which induce secondary negative symptoms does suggest that the improvement appears to occur to a greater extent to what was previously assumed. Further work examining the longitudinal course of negative symptoms in a study with clearly defined inclusion criteria relating to the persistence of negative symptoms, with appropriate controls for secondary negative symptoms, would provide stronger evidence for whether primary negative symptoms of the disorder are less stable than previously assumed.

Another limitation is that due to the substantial heterogeneity of the study designs, the fact that multiple arms of single studies were included which would naturally cluster together, and possible issues relating to the regression of the mean complicating the interpretation further, it was recognized that conducting an examination of publication bias important in typical meta-analytical studies (Higgins & Green, 2011) would have limited utility in this context. This being the case, such analysis was omitted so we cannot be certain as to whether publication bias influenced the results significantly. However, given a number of the studies were non-inferiority trials, dose–response studies, observational studies, and that control arms were used in this study as equivalent to experimental conditions, it would be unlikely that any publication bias would systematically inflate the overall effect sizes in the same manner as would typically be expected in a normal meta-analysis.

Finally, due to the lack of data, no-medication as a therapeutic option could not be evaluated, meaning it is not clear whether a reduction in negative symptoms would also occur in non-medicated patients. It is possible, however, that such an improvement could occur given there is some evidence to suggest that patients who do not immediately relapse upon termination of their antipsychotic regimen may experience improved global functioning over time (Harrow & Jobe, 2007).

### *Interpretation*

These findings are contrary both to the earliest conceptions of schizophrenia, which suggested that negative symptoms follow a path of progressive deterioration (Bleuler, 1951; Kraepelin, 1971), and our current understanding of negative symptoms which suggest that they are highly stable in the non-acute phase (Möller, 2007). While acknowledging that the improvement in

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

negative symptoms were relatively small in the TAU, non-drug intervention arms and typical antipsychotic study arms, the improvement of negative symptoms over time appear to lend support to the recovery model of schizophrenia, particularly given the relationship of these symptoms to psychosocial functioning (Norman *et al*. 2000; Warner, 2009).

Given the limitations of the within-group design, the effect sizes presented cannot be used as an assessment on the effectiveness of any one treatment. As highlighted earlier, a series of meta-analyses have been conducted to evaluate treatments for schizophrenia using more appropriate designs (i.e. Kurtz & Mueser, 2008; Leucht *et al*. 2009; Jauhar *et al*. 2014). Overall, these reviews have detected relatively limited treatment benefits for negative symptoms, contrasting with the large within-group effect sizes noted here in the example of second-generation antipsychotic and adjunctive drug medication trials. Further investigation into the TAU and placebo study arms indicate that the effect sizes of drug study control arms are substantially larger than non-drug study controls , which suggest there is something inherent in the methodologies employed which makes these drug studies more likely to detect and report symptoms improvements. Many drug studies used placebo, as opposed to TAU, so a placebo effect may account for at least part of this difference. However, while it has been noted that the placebo effect is an increasing issue in schizophrenia drug trials (Kinon *et al*. 2011), given the effect size differences between drug and non-drug studies are so large (ES = 0.67, in comparison to ES = 0.15) it suggests that other factors inherent to the design and assessment may also be important. Regardless, the highly varied nature and outcomes study arms which fall under the heading of TAU and placebos merits further investigation.

Disentangling how regression to the mean issue relates to negative symptoms in an exclusively outpatient sample is complex issue worthy of further consideration. Higher mean levels of negative symptoms at baseline did predict a greater reduction. However, the additional proportion of the variance explained over and above the intervention type and assessment scale used was fairly small (4.1%), suggesting that the regression to the mean may not be as large as one might typically expect. This could be due to a number of factors. First, primary negative symptoms are thought to be highly stable (Möller *et al*. 2007) so it is perhaps unlikely that a substantial fluctuation around the mean level of symptoms over time would be expected, presuming secondary factors are appropriately considered. Second, by omitting samples which contained inpatients at baseline (but not necessarily at study end), the patients were a lot less likely to have been recruited during their most severe phase of their disorder, further minimizing the regression to the mean effect (Morton & Torgerson, 2003).

When testing for sources of heterogeneity in the course of negative symptoms, only the impact of assessment scale type remained significant, after controlling for intervention type. In comparison to studies which used the PANSS or the BPRS, a significantly greater change in negative symptoms was detected in studies that used the SANS. The finding that the SANS is a more sensitive instrument to detect change is in line with recommendations outlined in the MATRICS consensus statement (Kirkpatrick *et al.* 2006) and is perhaps unsurprising given the scales focus on negative symptoms, despite the conceptual and methodological issues that the scale is recognized to have (Blanchard *et al*. 2011). No eligible studies used either the Clinical Assessment Interview for Negative Symptoms (Horan *et al.* 2011) or the Brief Negative Symptom Scale (Strauss *et al*. 2012), therefore it is unknown how these new scales compare.

Understanding how negative symptoms change over time requires further attention given the duration between time points was not found to be a significant predictor. However, with the considerable variability in treatment duration, post-treatment follow-up duration, and post-treatment provision between studies, this is perhaps not surprising. In longitudinal studies assessing negative symptoms over very long periods of time, there has been little evidence of a linear improvement towards symptom remission (Strauss *et al.* 2010), while the rate of recovery in schizophrenia remains low (Jääskeläinen *et al*. 2013). Overall, this suggests that the trajectory of this improvement may be complex. One possible explanation of the improvement uncovered could be the non-specific effects of increased attention derived from being involved in research. Patients with prominent negative symptoms are typically very socially isolated, so increased contact time with researchers in itself may provide some therapeutic benefit.

## Conclusions

Based on the available data of almost 6000 outpatients, negative symptoms of schizophrenia do not tend to be stable or deteriorate, but are instead likely to improve over time. This finding offers a further critique of the historical argument which suggests schizophrenia is a disorder of continual decline (Bleuler, 1950; Kraepelin, 1971) and instead provides further support to the recovery model of schizophrenia (Warner, 2009). Overall, these findings suggest that negative symptoms may not be as resistant to change as what has previously been assumed, and perhaps offer new hope to those who may experience such symptoms.

https://doi.org/10.1017/S0033291714002712 Published online by Cambridge University Press

## Acknowledgements

The authors thank Dr Stephen Bremer for statistical advice. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

## Declaration of Interest

None.

## References

**Adams DH, Kinon BJ, Baygani S, Millen BA, Velona I, Kollack-Walker S, Walling DP** (2013). A long- term, phase 2, multicenter, randomized, open-label, comparative safety study of pomaglumetad methionil (LY2140023 monohydrate) *versus* atypical antipsychotic standard of care in patients with schizophrenia. *BMC Psychiatry* **13**, 143.

**Addington J, Addington DG** (2000). Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophrenia Research* **41**, 47–56.

**Addington J, Addington DJ** (1991). Positive and negative symptoms of schizophrenia. Their course and relationship over time. *Schizophrenia Research* **5**, 51–59.

**Aguglia E, De Vanna M, Onor ML, Ferrara DG** (2002). Insight in persons with schizophrenia effects of switching from conventional neuroleptics to atypical antipsychotics. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **26**, 1229–1233.

**Alptekin K, Erkoc S, Gogus AK, Kultur S, Mete L, Ucok A, Yazici KMG** (2005). Disability in schizophrenia: clinical correlates and prediction over 1-year follow-up. *Psychiatry Research* **135**, 103–111.

**Alvarez E, Ciudad A, Olivares JM, Bousono M, Gomez JCG** (2006). A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. *Journal of Clinical Psychopharmacology* **26**, 238–249.

**Amell R, Llandrich JG** (2008). Validity of a social skills training program for schizophrenic patients. *Actas Espanolas de Psiquiatria* **36**, 123–132.

**Andreasen NC** (1983). *Scale for the Assessment of Negative Symptoms*. University of Iowa: Iowa City.

**Arango C, Garibaldi G, Marder R** (2013). Pharmacological approaches to treating negative symptoms: a review of clinical trials. *Schizophrenia Research* **150**, 346–352.

**Bales A, Peterson MJ, Ojha S, Upadhaya K, Adhikari B, Barrett BG** (2009). Associations between betel nut (Areca catechu) and symptoms of schizophrenia among patients in Nepal: a longitudinal study. *Psychiatry Research* **169**, 203–211.

**Becker BJ** (1988). Synthesizing standardized mean-change measures. *British Journal of Mathematical and Statistical Psychology* **41**, 257–278.

**Behere RV, Arasappa R, Jagannathan A, Varambally S, Venkatasubramanian G, Thirthalli J, Subbakrishna DK, Nagendra HR, Gangadhar BNG** (2011). Effect of yoga therapy on facial emotion recognition deficits, symptoms and functioning in patients with schizophrenia. *Acta Psychiatrica Scandinavica* **123**, 147–153.

**Bhowmick S, Hazra A, Ghosh MG** (2010). Amisulpride *versus* olanzapine in the treatment of schizophrenia in Indian patients: randomized controlled trial. *Australian and New Zealand Journal of Psychiatry* **44**, 237–242.

**Bio DS, Gattaz WFG** (2011). Vocational rehabilitation improves cognition and negative symptoms in schizophrenia. *Schizophrenia Research* **126**, 265–269.

**Blanchard JJ, Kring AM, Horan WP, Gur R** (2011). Toward the next generation of negative symptom assessments: the collaboration to advance negative symptom assessment in schizophrenia. *Schizophrenia Bulletin* **37**, 291–299.

**Bleuler E** (1950). *Dementia Praecox and the Group of Schizophrenias*. New York: International Universities Press.

**Bobes J, Ciudad A, Alvarez E, San L, Polavieja P, Gilaberte I** (2009). Recovery from schizophrenia: results from a 1-year follow-up observational study of patients in symptomatic remission. *Schizophr Research* **115**, 58–66.

**Bodkin J, Siris SG, Bermanzohn PC, Hennen J, Cole JOG** (2005). Double-blind, placebo-controlled, multicenter trial of selegiline augmentation of antipsychotic medication to treat negative symptoms in outpatients with schizophrenia. *American Journal of Psychiatry* **162**, 388–390.

**Buchanan RW** (2007). Persistent negative symptoms in schizophrenia: an overview. *Schizophrenia Bulletin* **33**, 1013–1022.

**Carpenter WT, Heinrichs DW, Alphs LD** (1985). Treatment of negative symptoms. *Schizophrenia Bulletin* **11**, 440–452.

**Chiolero A, Paradis G, Rich B, Hanley JA** (2013). Assessing the relationship between the baseline value of a continuous variable and subsequent change over time. *Frontiers in Pulblic Health* **1** (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3854983/). Accessed 11 November 2014.

**Chouinard G, Annable L, Serrano M, Albert JM, Charette R** (1975). Amitriptyline-perphenazine interaction in ambulatory schizophrenic patients. A controled study of drug interaction. *Archives of General Psychiatry* **32**, 1295–1307.

**Crawford MJ, Killaspy H, Barnes TR, Barrett B, Byford S, Clayton K, Dinsmore J, Floyd S, Hoadley A, Johnson T, Kalaitzaki E, King M, Leurent B, Maratos A, O'neill FA, Osborn D, Patterson S, Soteriou T, Tyrer P, Waller D** (2012). Group art therapy as an adjunctive treatment for people with schizophrenia: a randomised controlled trial (MATISSE). *British Medical Journal* **344** (http://www.bmj.com/content/344/bmj.e846).

**Dersimonian R, Laird N** (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177–188.

**Dollfus S, Petit MG** (1995). Stability of positive and negative symptoms in schizophrenic patients: a 3-year follow-up study. *European Psychiatry* **10**, 228–236.

**Dossenbach M, Erol A, Kessaci MEM, Shaheen MO, Sunbol MM, Boland J, Hodge A, O'Halloran RA, Bitter IG** (2004). Effectiveness of antipsychotic treatments for schizophrenia: interim 6-month analysis from a prospective observational study (IC-SOHO) comparing olanzapine, quetiapine, risperidone, and haloperidol. *Journal of Clinical Psychiatry* **63**, 312–321.

**Eaton WW, Thara R, Federman B, Melton B, Liang KYJ** (1995). Structure and course of positive and negative

symptoms in schizophrenia. *Archives of General Psychiatry* **52**, 127–134.

**Fenton WS, McGlashan THJ** (1991). Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Archives of General Psychiatry* **48**, 978–986.

**Fleischhacker WW, Eerdekens M, Karcher K, Remington G, Llorca PM, Chrzanowski W, Martin S, Gefvert OJ** (2003). Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *Journal of Clinical Psychiatry* **64**, 1250–1257.

**Gaebel W, Riesbeck M, Wolwer W, Klimke A, Eickhoff M, Von Wilmsdorff M, Jockers-Scherubl MC, Kuhn KU, Lemke M, Bechdolf A, Bender S, Degner D, Schlosser R, Schmidt LG, Schmitt A, Jager M, Buchkremer G, Falkai P, Klingberg S, Kopcke W, Maier W, Hafner H, Ohmann C, Salize HJ, Schneider F, Moller HJG** (2007). Maintenance treatment with risperidone or low-dose haloperidol in first-episode schizophrenia: 1-year results of a randomized controlled trial within the German research network on schizophrenia. *Journal of Clinical Psychiatry* **68**, 1763–1774.

**Goff DC, Herz L, Posever T, Shih V, Tsai G, Henderson DC, Freudenreich O, Evins A, Yovel I, Zhang H, Schoenfeld DG** (2005). A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. *Psychopharmacology* **179**, 144–150.

**Gorna K, Jaracz K, Rybakowski F, Rybakowski J** (2008). Determinants of objective and subjective quality of life in first-time-admission schizophrenic patients in Poland: a longitudinal study. *Quality of Life Research* **17**, 237–247.

**Harrow M, Jobe TH** (2007). Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: a 15-year multi follow-up study. *Journal of Nervous and Mental Disease* **195**, 406–414.

**Hayes RL, Halford WK, Varghese FTJ** (1995). Social skills training with chronic schizophrenic patients: effects on negative symptoms and community functioning. *Behavior Therapy* **26**, 433–449.

**Hecht EM, Landy C** (2012). Alpha-2 receptor antagonist add-on therapy in the treatment of schizophrenia; a meta-analysis. *Schizophrenia Research* **134**, 202–206.

**Higgins JPT, Green S** (2011). *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0. The Cochrane Collaboration (www.cochrane-handbook.org). Accessed 11 November 2014.

**Hirsch SR, Kissling WB, Uml J, Power A, O'connor RJ** (2002). A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *Journal of Clinical Psychiatry* **63**, 516–523.

**Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ** (2011). Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophrenia Research* **132**, 140–145.

**Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J** (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin* **39**, 1296–1306.

**Jauhar S, Mckenna PJ, Radua J, Fung E, Salvador R, Laws KR** (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry* **204**, 20–29.

**Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides JJ** (2011). A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *Journal of Clinical Psychiatry* **72**, 349–355.

**Kane JM, Yang R, Youakim JM** (2012). Adjunctive armodafinil for negative symptoms in adults with schizophrenia: a double-blind, placebo-controlled study. *Schizophrenia Research* **135**, 116–122.

**Kaphzan H, Ben-Shachar D, Klein E** (2014). Entacapone augmentation of antipsychotic treatment in schizophrenic patients with negative symptoms; a double-blind placebo-controlled study. *International Journal of Neuropsychopharmacology* **17**, 337–340.

**Kasckow JW, Twamley E, Mulchahey JJ, Carroll B, Sabai M, Strakowski SM, Patterson T, Jeste DV** (2001). Health-related quality of well-being in chronically hospitalized patients with schizophrenia: comparison with matched outpatients. *Psychiatry Research* **103**, 69–78.

**Kay SR, Flszbein A, Opfer LA** (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261.

**Kinon BJ, Potts AJ, Watson SB** (2011). Placebo response in clinical trials with schizophrenia patients. *Current Opinion in Psychiatry* **24**, 107–113.

**Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR** (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin* **32**, 214–219.

**Klingberg S, Wolwer W, Engel C, Wittorf A, Herrlich J, Meisner C, Buchkremer G, Wiedemann GJ** (2011). Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: results of the randomized clinical TONES study. *Schizophrenia Bulletin* **37**, 98–110.

**Kraepelin E** (1971). *Dementia Praecox and Paraphrenia (1919)*. Translated by Barclay RM; edited by Robertson GM. Robert E Krieger: New York.

**Kurtz MM, Mueser KT** (2008). A meta-analysis of controlled research on social skills training for schizophrenia. *Journal of Consulting and Clinical Psychology* **76**, 491–504.

**Kurtz MM, Richardson CL** (2012). Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophrenia Bulletin* **38**, 1092–1104.

**Lasser A, Dirks B, Nasrallah H, Kirsch C, Gao J, Pucci L, Knesevich A, Lindenmayer JP** (2013). Adjunctive lisdexamfetamine dimesylate therapy in adult outpatients with predominant negative symptoms of schizophrenia: open-label and randomized-withdrawal phases. *Neuropsychopharmacology* **38**, 2140–2149.

**Lecrubier Y, Quintin P, Bouhassira M, Perrin E, Lancrenon SG** (2006). The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta Psychiatrica Scandinavica* **114**, 319–327.

**Leucht S, Arbter D, Engel RR, Kissling W, Davis JM** (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry* **14**, 429–447.

**Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D** (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology* **62**, e1–e34.

**Liberman RP, Wallace CJ, Blackwell G, Kopelowicz A, Vaccaro JV, Mintz J** (1998). Skills training *versus* psychosocial occupational therapy for persons with persistent schizophrenia. *American Journal of Psychiatry* **155**, 1087–1091.

**Lieberman A, Dunbar G, Segreti C, Girgis R, Seoane F, Beaver S, Duan N, Hosford A** (2013). A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology* **38**, 968–975.

**Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK** (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* **353**, 1209–1223.

**Liu F, Guo X, Wu R, Ou J, Zheng Y, Zhang B, Xie L, Zhang L, Yang L, Yang S, Yang J, Ruan Y, Zeng Y, Xu X, Zhao J** (2014). Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double blind, randomized, controlled trial. *Schizophrenia Research* **153**, 169–176.

**Loebel AD, Khanna S, Rajadhyaksha S, Siu CO, Giller E, Potkin SGJ** (2007). Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. *Journal of Clinical Psychiatry* **68**, 1333–1338.

**Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot OG** (1997). Amisulpride *versus* placebo in the medium-term treatment of the negative symptoms of schizophrenia. *British Journal of Psychiatry* **170**, 18–22.

**Lyne JP, Kinsella A, O'Donoghue B** (2012). Can we combine symptom scales for collaborative research projects? *Journal of Psychiatric Research* **46**, 233–238.

**Malhi GS, Green M, Fagiolini A, Peselow ED, Kumari V** (2008). Schizoaffective disorder: diagnostic issues and future recommendations. *Bipolar Disorders* **10**, 215–230.

**Marder SR, Glynn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, Mintz J, Liberman RP, Blair KEJ** (2003). Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *American Journal of Psychiatry* **160**, 1405–1412.

**Meltzer HY, Bobo WV, Lee MA, Cola P, Jayathilake KG** (2010). A randomized trial comparing clozapine and typical neuroleptic drugs in non-treatment-resistant schizophrenia. *Psychiatry Research* **177**, 286–293.

**Möller HJ** (2007). Clinical evaluation of negative symptoms in schizophrenia. *European Psychiatry* **22**, 380–386.

**Morris SB** (2000). Distribution of the standardized mean change effect size for meta-analysis on repeated measures. *British Journal of Mathamatical and Statistical Psychology* **53**, 17–29.

**Morton V, Torgerson DJ** (2003). Effect of regression to the mean on decision making in health care. *British Medical Journal* **326**, 1083.

**NCCMH** (2010). *Schizophrenia: The NICE Guideline on Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care*, updated edition. The British Psychological Society and the Royal College of Psychiatrists: London.

**Norman RM, Malla AK, Mclean T, Voruganti LP, Cortese L, Mcintosh E, Cheng S, Rickwood A** (2000). The relationship of symptoms and level of functioning in schizophrenia to general wellbeing and the Quality of Life Scale. *Acta Psychiatrica Scandinavica* **102**, 303–309.

**Olie JP, Spina E, Murray S, Yang RG** (2006). Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. *International Clinical Psychopharmacology* **21**, 143–151.

**Oshima I, Yoshio M, Yoshimasa I** (2003). Institutionalisation and schizophrenia in Japan: social environments and negative symptoms Nationwide survey of in-patients. *British Journal of Psychiatry* **183**, 50–56.

**Overall JE, Gorham DR** (1962). The brief psychiatric rating scale. *Psychological Reports* **10**, 799–812.

**Pach J, Finkbeiner T, Glaser T, Haug J, Osterheider M, Tegeler JJ** (1998). Positive and negative symptoms in chronic schizophrenic patients under maintenance therapy with flupenthixol decanoate for a twelve month perioid. *Fortschritte der Neurologie Psychiatrie* **66**, 442–449.

**Peet M, Horrobin DFG** (2002). A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *Journal of Psychiatric Research* **36**, 7–18.

**Pinto R, Bannerjee A, Ghosh N** (1979). A double-blind comparison of flupenthixol decanoate and fluphenazine decanoate in the treatment of chronic schizophrenia. *Acta Psychiatrica Scandinavica* **60**, 313–322.

**Pogue-Geile MF, Harrow MG** (1985). Negative symptoms in Schizophrenia: their longitudinal course and prognostic importance. *Schizophrenia Bulletin* **11**, 427–439.

**Priebe S, Mccabe R, Bullenkamp J, Hansson L, Lauber C, Martinez-Leal R, Rossler W, Salize H, Svensson B, Torres-Gonzales F, Van Den Brink R, Wiersma D, Wright DJ** (2007). Structured patient-clinician communication and 1-year outcome in community mental healthcare: cluster randomised controlled trial. *British Journal of Psychiatry* **191**, 420–426.

**Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Breier A, Tollefson GD** (2000). Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Archives of General Psychiatry* **57**, 249–258.

**Ravanic DB, Dejanovic SMD, Janjic V, Jovic SD, Milovanovic DR, Jakovljevic V, Pantovic V, Ravanic B, Pantovic M, Pantovic MMG** (2009). Effectiveness of

clozapine, haloperidol and chlorpromazine in schizophrenia during a five-year period. *Arquivos de Neuro-Psiquiatria* **67**, 195–202.

**Richardson P, Jones K, Evans C, Stevens P, Rowe AG** (2007). Exploratory RCT of art therapy as an adjunctive treatment in schizophrenia. *Journal of Mental Health* **16**, 483–491.

**Schoemaker JH, Jansen WT, Schipper J, Szegedi A** (2014). The selective glycine uptake inhibitor org 25935 as an adjunctive treatment to atypical antipsychotics in predominant persistent negative symptoms of schizophrenia: results from the GIANT trial. *Journal of Clinical Psychopharmacology* **34**, 190–198.

**Semiz UB, Cetin M, Basoglu C, Ebrinc S, Uzun O, Herken H, Balibey H, Algul A, Ates AG** (2007). Clinical predictors of therapeutic response to clozapine in a sample of Turkish patients with treatment-resistant schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **31**, 1330–1336.

**Singh SP, Singh V, Kar N, Chan K** (2010). Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *British Journal of Psychiatry* **197**, 174–179.

**Statacorp L** (2009). *Stata: release 11*, StataCorp LP.

**Strauss GP, Harrow M, Grossman LS, Rosen CG** (2010). Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. *Schizophrenia Bulletin* **36**, 788–799.

**Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, Mcmahon RP, Catalano LT, Culbreth AJ, Carpenter WT, Kirkpatrick B** (2012). Next-generation negative symptom assessment for clinical trials: validation of the brief negative symptom scale. *Schizophrenia Research* **142**, 88–92.

**Sumiyoshi T, Park S, Jayathilake K, Roy A, Ertugrul A, Meltzer HY** (2007). Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophrenia Research* **95**, 158–168.

**Taiminen TJ, Syvalahti E, Saarijarvi S, Niemi H, Lehto H, Ahola V, Salokangas RKRG** (1997). Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *International Clinical Psychopharmacology* **12**, 31–35.

**Tuominen HJ, Tiihonen J, Wahlbeck K** (2005). Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. *Schizophrenia Research* **72**, 225–234.

**Turkington D, Sensky T, Scott J, Barnes TRE, Nur U, Siddle R, Hammond K, Samarasekara N, Kingdon DG** (2008). A randomized controlled trial of cognitive-behavior therapy for persistent symptoms in schizophrenia: a five-year follow-up. *Schizophrenia Research* **98**, 1–7.

**Ucok A, Serbest S, Kandemir PEG** (2011). Remission after first-episode schizophrenia: results of a long-term follow-up. *Psychiatry Research* **189**, 33–37.

**Voruganti LP, Awad AG, Parker G, Forrest C, Usmani Y, Fernando ML, Senthilal S** (2007). Cognition, functioning and quality of life in schizophrenia treatment: results of a one-year randomized controlled trial of olanzapine and quetiapine. *Schizophrenia Research* **96**, 146–155.

**Wykes T, Huddy V, Cellard C, Mcgurk SR, Czobor P** (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry* **168**, 472–485.

**Xiang Y, Weng Y, Li W, Gao L, Chen G, Xie L, Chang Y, Tang WK, Ungvari GSJ** (2006). Training patients with schizophrenia with the community re-entry module: a controlled study. *Social Psychiatry and Psychiatric Epidemiology* **41**, 464–469.

**Zhang Z, Xu X, Ni H** (2013). Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Critical Care* **17**, R2 (http://ccforum.com/content/17/1/R2). Accessed 11 November 2014.

**Zoccali R, Muscatello MR, Bruno A, Cambria R, Mico U, Spina E, Meduri MG** (2007). The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophrenia Research* **93**, 109–116.