

The relationship between negative symptoms and depression in schizophrenia

Krynicky, C. R.; Upthegrove, R.; Deakin, J. F.W.; Barnes, T. R.E.

DOI:
[10.1111/acps.12873](https://doi.org/10.1111/acps.12873)

Document Version
Peer reviewed version

Citation for published version (Harvard):
Krynicky, CR, Upthegrove, R, Deakin, JFW & Barnes, TRE 2018, 'The relationship between negative symptoms and depression in schizophrenia: A systematic review', *Acta Psychiatrica Scandinavica*, vol. 137, no. 5, pp. 380-390. <https://doi.org/10.1111/acps.12873>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 13/04/2018
This is the peer reviewed version of the following article:
Krynicky CR, Upthegrove R, Deakin JFW, Barnes TRE. The relationship between negative symptoms and depression in schizophrenia: a systematic review.,
which has been published in final form at <https://doi.org/10.1111/acps.12873>.
This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

**The relationship between negative symptoms and depression in schizophrenia –
A systematic review**

Carl R. Krynicki, Rachel Upthegrove, Bill J. F. Deakin, Thomas R. E. Barnes

Abstract

Objective: Provide an update on the evidence base for the nature of the relationship between negative symptoms and depressive features in people with schizophrenia, and propose new models that reflect their complex relationship.

Method: A systematic review following PRISMA guidelines. 2210 articles were identified from EMBASE, PsychInfo and Medline and a further 2 articles were hand searched from references. 27 met inclusion criteria and were included in the review.

Results: In schizophrenia, primary evidence suggests symptoms of low mood, suicidal ideation and pessimism have more specificity for depression whereas alogia and blunted affect may have more specificity as negative symptoms. Anhedonia, anergia and avolition may be common to both.

Conclusion: It may be possible to further distinguish depressive features from negative symptoms in schizophrenia when detailed phenomenology is considered. However, in a proposed dimensional model, these two domains continue to share certain phenomena, highlighting their close relationship.

Key words: Depression, schizophrenia

Summations

- Symptoms such as low mood, suicidal ideation and pessimism are cited within a depressive domain, whereas symptoms such as alogia and blunted affect appear to indicate negative symptoms. Anhedonia, anergia and avolition occur across both domains.
- Detailed understanding of underlying phenomenology may provide potential treatment targets as well informing future research assessing underlying aetiological mechanisms.

Considerations

- Research methodologies of included studies were highly variable, leaving interpretation of the results open to bias.
- Future studies should focus on employing appropriate scales to assess depression, and consider the negative symptoms as two dissociable sub-domains (avolition-apathy and expressive-deficit).

Introduction

Schizophrenia has been conceptualised as a neuro-developmentally mediated, cognitive illness marked by a more unfavourable outcome than affective disorders (1). Positive and negative symptoms and cognitive dysfunction are core features of the illness, however there is a phenomenological overlap between schizophrenia and mood disorders (2); mood symptoms are common features in prodromal psychosis and established schizophrenia (3), while psychotic symptoms frequently occur with severe mood disorders. Such observations, as well as burgeoning biological evidence (4, 5), challenge the Kraepelinian dichotomy. One area of perhaps neglected phenomenological enquiry is negative symptoms; negative symptoms may present variously as a loss of motivation to act and a lack of the elements that make up the normal repertoire of social and emotional responsiveness (6), yet these are also commonly seen in depression (7).

Andreasen (8) characterised negative symptoms as consisting of affective blunting or flattening, alogia, anhedonia/asociality and avolition/apathy and attention; although attentional deficits may indicate cognitive impairment rather than a manifestation of a negative symptoms. Much of the earlier research exploring negative symptoms has assumed that they form one discrete syndrome. However, factor analyses have isolated two sub-domains within negative symptoms (9, 10) namely avolition-amotivation and expressive deficits. The avolition-amotivation sub-domain is considered to be formed of the symptoms; avolition, asociality and anhedonia, whereas the diminished expression sub-domain comprises blunted affect and alogia (11-13).

Depression is a mood disorder that is characterised by low mood and anhedonia (14). Affective symptoms have been recognised as occurring commonly in non-affective psychosis, in 50%- 80% of patients at some point during their illness (15,

16). Previously, Siris et al. (17) found that half of individuals with post-psychotic depression also met criteria for negative symptoms, implying a syndromal overlap between depressive and negative symptoms. However Addington et al. (18) designed the Calgary Depression Scale for Schizophrenia to assess depression separately from negative symptoms and also from positive symptoms and extrapyramidal symptoms such as parkinsonism.

Previous models have conceptualised depression and negative symptoms as belonging to distinct and separate clinical syndromes (19-23). Within a dimensional approach to psychoses, a model of overlapping domains with distinct presentations allows further exploration of the heterogeneity involved. Initially presented as three domains of reality distortion, psychomotor poverty and disorganization syndrome (24), more recently mood symptoms have been included in five factor models; positive symptoms, negative symptoms, depression, mania and cognitive (25). These models of symptoms of psychoses allow for co-morbidity in more than one domain, with an individual patient presenting with varying degrees of symptom severity in each domain.

The exact nature of the relationship between depression and negative symptoms in a 'non-affective' psychotic illness such as schizophrenia remains uncertain. Identifying depression in schizophrenia and treating this symptom domain is essential given that depression in schizophrenia has been associated with poor prognosis and suicide (3, 26). Understanding this heterogeneity further is potentially important for the elucidation of the underlying aetiological mechanisms and the development of better, targeted, treatments.

Aim of the study

The aim of this systematic review was to provide a novel and up-to-date review of the evidence for the phenomenological co-occurrence of depression and negative symptoms in schizophrenia.

Method

A systematic search and review following the PRISMA guidelines (27) was conducted. We limited our search to studies examining depression and negative symptoms in schizophrenia and excluded studies looking at other conditions. There were no limits put on the origin or date of a publication.

Inclusion criteria

1. Studies that aimed to report the relationship between negative and depressive symptoms in schizophrenia.
2. Studies that were published in English.

Exclusion criteria

1. Review articles, letters to editors and presentation abstracts
2. Papers that reported depression and only other (non-negative) symptom domains (e.g. positive symptoms and depression; social functioning, insight)

The following databases were searched on 05/01/2018: MEDLINE, PSYCHINFO, and EMBASE. The following search terms were used: "SCHIZOPHRENIA"; or

“SCHIZOPHRENIA, CATACTONIC” or “SCHIZOPHRENIA CHILDHOOD” or “SCHIZOPHRENIA, DISORGANISED” or “SCHIZOPHRENIA, PARANOID” or “PSYCHOTIC DISORDERS” or “SCHIZOPHREN*” or “PSYCHOSIS” or “PSYCHOSES” or “FIRST EPISODE PSYCHOSIS” and “DEPRESSION” or “DEPRESSIVE DISORDER” or “DYSTHYMIC DISORDER” or “DEPRESSIVE DISORDER, MAJOR” or “TREATMENT RESISTANT” or “DEPRESSION” or “AFFECTIVE DISORDER” or “MOOD DISORDERS” and “NEGATIVE SYMPTOM” or “ANHEDONIA” or “APATHY” or “ALOGIA” or “ASOCIALITY” or “AFFECTIVE FLATTENING” or “BLUNTED AFFECT” or “AVOLITION” or “SOCIAL WITHDRAWAL” or “LOSS MOTIVAT*” or “LACK MOTIVAT*” (see supplementary table 1 for the full search strategy)

Two reviewers (CRK and RU) independently reviewed all the papers screened and agreed on which papers should be included in the review (see Table 1).

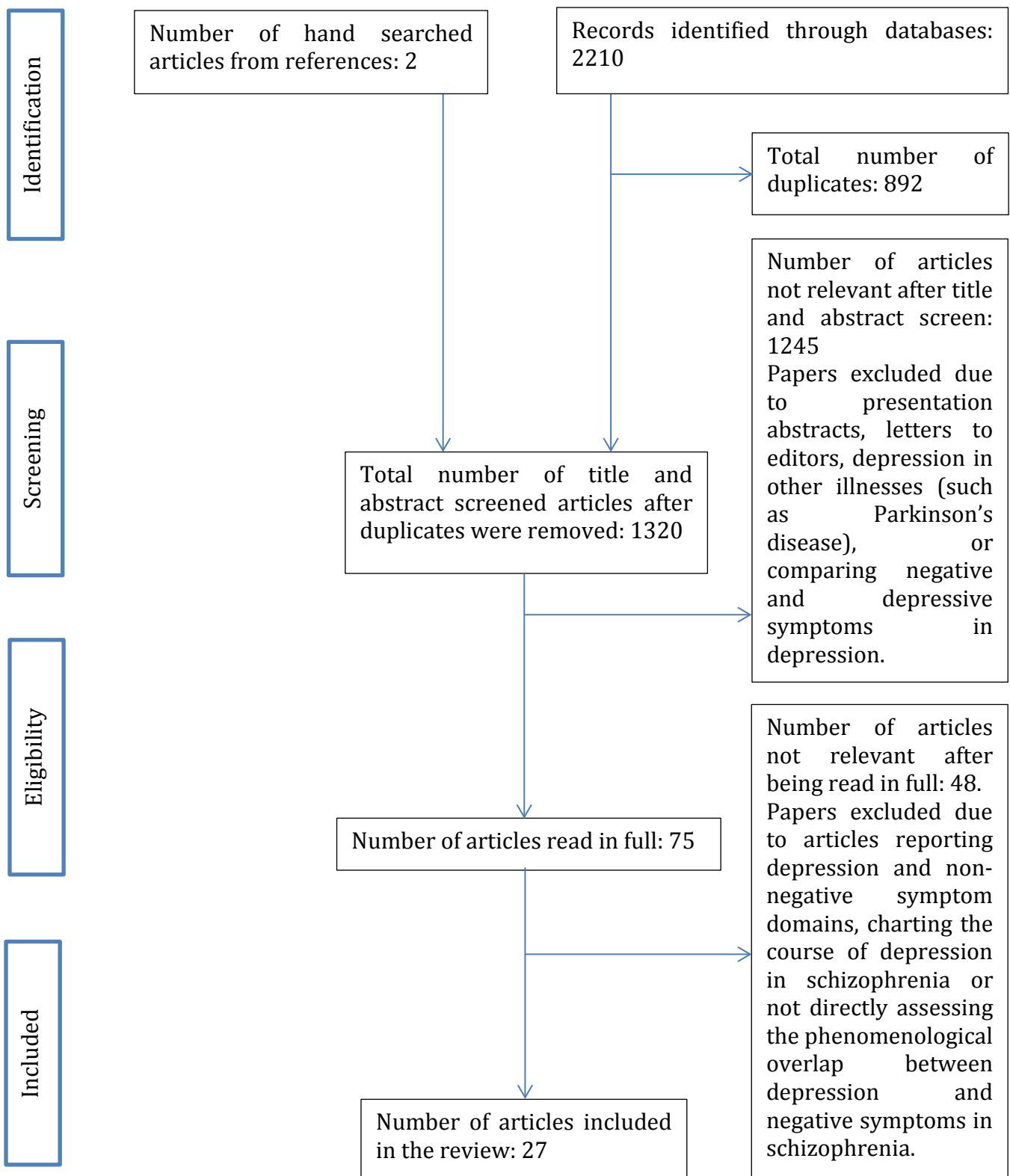


Figure 1 : Flow diagram of studies included in the systematic review

| Author | Year | Number of participants (Inc. gender) | Population | Depression scale | Negative symptoms scale | Antidepressant usage | Conclusions | Other information |
|-----------------------|------|--|-------------------------|------------------|---------------------------------------|----------------------|---|-------------------|
| Whiteford et al. (28) | 1987 | 40 male patients with chronic schizophrenia | Outpatients | HRSD, | SANS | Unknown | Nx and Dx overlap on loss of energy, drive and interest and anhedonia/asociality, but can be differentiated on features such as poverty of thought and speech, and poor attention/concentration, which were related to Nx but not Dx. | Cross-sectional |
| Barnes et al. (29) | 1989 | 194 chronic schizophrenia | Inpatients | BDI | SANS (specific rating for Anhedonia). | Unknown | Confirmed a Dx syndrome which was distinct from Nx symptoms and was not a result of pharmacotherapy. | Cross-sectional |
| Pogue-Geile (30) | 1989 | 44 (40 with schizophrenia and 4 schizoaffective) | Outpatient | SADS-L; BDI, | SANS | Unknown | There was no significant difference between Nx and Dx in schizophrenia. | Cross-sectional |
| Kulhara et al. (31) | 1989 | 95 patients with schizophrenia | Patients were referred. | BPRS | BPRS (total score); SANS; SAPS | Unknown | Retardation, lack of energy and slowness were associated with Nx. Depressed mood was associated with Dx. | Cross-sectional |
| Ragin et al. (32) | 1989 | 25 (12 schizophrenia, 13 depressed) | Inpatient, and then | SADS | TLC | Unknown | During inpatient admission, Dx patients experienced more poverty of speech than | Longitudinal |

| | | | | | | | | |
|---------------------|------|--|-----------------------------|---|---|---|---|------------------------------|
| | | patients) | followed up after discharge | | | | SCZ patients. At follow up, poverty of speech increased in SCZ patients but stayed the same in Dx patients. | |
| Newcome et al. (33) | 1990 | 69 schizophrenia (all male) | Unmedicated inpatients | BPRS:DEP (depressed mood, guilt, anxiety and somatic concern); HRSD | BPRS:NEG (blunted affect, emotional withdrawal, motor retardation). | All unmedicated | High association between Nx measures and Dx measures. Other items reflecting other aspects of Dx did correlate with the Nx measures. | Retrospectively drawn sample |
| Koreen et al. (16) | 1993 | 70 patients with schizophrenia/schizoaffective (39 male, 31 female). | Inpatients | Extracted scores on the HDRS | SADS; SANS; CGI-S | Following baseline assessment, patients prescribed antidepressants and antipsychotics | Dx are present and prevalent in the first episode and occur concurrently with psychotic symptoms and resolves as the psychotic episode remits. Dx is a core feature of schizophrenia and correlates with Nx and Px. | Prospective |
| Kibel et al. (34) | 1993 | 73 schizophrenia (51 male, 22 female) | Inpatients | Montgomery - Asberg Depression rating scale | SANS; NSRS; PANSS (total), Manchester scale, Montgomery | Unknown | Subjective sadness, pessimism and suicidal intent belong to the Dx. Observed sadness, lassitude and inability to feel were more strongly associated with Nx. | Cross-sectional |

| | | | | | | | | | | |
|---------------------|------|--|------------|---------------------------------------|-----|---|--|---|------------------------------|--|
| | | | | | | Schizophrenia Scale. | | | | |
| Tharyan et al. (35) | 1994 | 46 patients with schizophrenia | Unknown | HDRS | | SANS | Initially unmedicated and then medicated | Depressed patients showed fewer negative symptoms than non-depressed. | Longitudinal | |
| Sax et al. (36) | 1996 | 17 with schizophrenia (including schizophreniform and psychosis not specified), 25 with depression | Inpatient | HRSD | | SANS; SAPS | Unknown | Dx and Nx correlated on poor motivation, social withdrawal and anhedonia, which were not attributable to any drug effects. | Cross sectional | |
| Nakaya et al. (37) | 1997 | 89 with schizophrenia/schizophreniform (39 male, 47 female) | Inpatients | HRSD (17 item); PANSS depression item | (17 | PANSS (total negative symptom subscale) | Unknown | There was a lack of association between improvement of Dx and Nx. | Prospective and longitudinal | |
| Nakaya et al. (38) | 1998 | 86 patients with schizophrenia or schizophreniform. (39 male, 47 female). | Inpatients | HRSD (17 item version) | (17 | PANSS (total negative symptom subscale) | Unknown | Differences in the composition of the Dx syndrome were observed in the acute and chronic phase of schizophrenia. Dx unrelated to Px and Nx. | Prospective and longitudinal | |
| Zisook et al. (39) | 1999 | 60 patients | Outpatient | HDRS | and | SANS and | Medicated | Severity of Dx did not | Cross- | |

| | | | | | | | | |
|--------------------|------|---|---------------------------------|---|--|---------------------------------------|--|------------------------------------|
| al. (39) | | with schizophrenia, 60 healthy controls | nts | BPRS | BPRS | | correlated with severity of Nx. | sectional |
| Baynes et al. (40) | 2000 | 120 chronic schizophrenia (78 male, 42 female) | with out-patients | BDI; HDRS; CGISS; BPRS (anxiety/depression items) | SANS | No antidepressants | No association between Dx and Nx in schizophrenia. Dx are more common in the active illness. | Cross-sectional |
| Romney et al. (22) | 2001 | 54 schizophrenia (55 male, 26 female) | 36 in-patients; 45 out-patients | BDI; HRSD; MDI; | PANSS (total negative subscale score); PAS; SAS; Maine scale | MDD patients took antidepressants | Anhedonia is more closely aligned with Dx. | Cross-sectional - Factor analysis |
| Tapp et al. (41) | 2001 | 104 schizophrenia and depression | Inpatients | HRSD | SANS; BPRS (total negative subscale) | Unknown | Dx are prevalent during acute psychosis and are reduced following treatment with antipsychotic medication. | Experimental - double blind trial. |
| Muller et al. (42) | 2002 | 57 schizophrenia, 4 schizoaffective) (53 Male, 36 female) | Inpatients | CDSS | PANSS (total negative subscale) | 14% patients received antidepressants | Dx is heterogeneous and occurs in schizophrenia. These symptoms are separate from emotional blunting and emotional blunting is independent from Dx. Affective blunting was observed in patients with | Cross-sectional |

| | | | | | | | | | |
|------------------------|------|---|--------------------------------|---|-----------|---------------------------------|---------------------------|---|-------------------------------------|
| | | | | | | | | residual and disorganised schizophrenia. | |
| Oosthuizen et al. (43) | 2002 | 80 (41 male, 39 female) | schizophrenia/schizophreniform | Unknown | PANSS - D | PANSS (total negative subscale) | Antidepressants were used | Dx were common in the first episode and were also independent from Nx. | Experimental - open labelled trial. |
| Bottlender et al. (44) | 2003 | 76 (33 schizophrenia, 43 depression) | Inpatient | Montgomery-Asberg Depression Rating scale | | SANS | Unknown | For Dx patients, Nx emerged for within 3 months prior to hospitalisation. In patients with SCZ, Nx were present for 12 months prior to admission and were more enduring than in those with Dx. Also, Nx in Dx patients was associated with Dx symptoms but not in SCZ patients. | Cross sectional and longitudinal |
| Maggini et al. (45) | 2004 | 128 with chronic schizophrenia (87 male, 41 female) | Unknown | CDSS | | SANS; SAPS; SENS | Unknown | Dx patients with schizophrenia showed higher scores for Px, anhedonia, asociality, cognitive overload, basic emotional impairment and heightened awareness of functional deficits. Dx did not correlate with Nx. | Cross-sectional |
| Hafner et al. (46) | 2005 | 130 first admission patients with | first admission | Retrospective Assessment | | IRAOS | 81% of schizophrenia | Dx and Nx are prominent in the prodromal stages of Dx and schizophrenia and | Cross-sectional |

| | | | | | | | | |
|-----------------------|------|--|---|--|---------------------------------|---|--|-------------------|
| | | schizophrenia. 130 with depression. 130 healthy controls | patients | t of the Onset of Schizophrenia | | patients and 79% of depressed were drug naïve. | transition to psychosis or depression later in the illness. | |
| Hafner et al. (47) | 2005 | 130 with schizophrenia (51%male, 49% female), 130 depressed (51%male, 49% female) and 130 controls (51%male, 49% female) | Patients from Mental health institution | IRAOS | IRAOS | Most were medication naïve (both antipsychotic and antidepressants) | Dx and schizophrenia begin with combined symptomology consisting of Dx and increasing impairment. | Cross-sectional |
| Rocca et al. (48) | 2005 | 78 (46 males and 32 females) with schizophrenia | Outpatient | CDSS | PANSS (total negative subscale) | Unknown | Nx were separate from those of Dx. Also, outcome for patients with Dx and Nx was less favourable. Dx and Nx did not share the same pattern of clinical and cognitive predictors. | Cross-sectional |
| Uptegrove et al. (15) | 2010 | 92 with FEP (87% - non-affective psychosis, 13% - affective psychosis. | EIS | Prodromal depression: SCAN; Baseline and follow up | PANSS (total negative subscale) | Unknown | Dx occurs, waxes and wanes throughout early psychosis and predicts illness with prodromal Dx predicting Dx in the early course and future Dx episodes throughout the | Prospective study |

| | | | | depression: CDSS | | | course of illness. | |
|------------------------|------|--|--|---|---|--|---|-----------------------------------|
| Majadas et al. (49) | 2012 | 90 (59% male, 41% female - 73 with schizophrenia, 2 schizophreniform and 15 with schizoaffective disorder) | Outpatient clinic | CDSS | PANSS (total negative subscale); SANS; SUMD | Patients with a diagnosis of depression or treated with antidepressants were excluded. | Dx is frequent in the stable phase of schizophrenia and is associated with greater severity of illness. Dx is indicative of greater severity of the illness. Dx and Nx are poorly associated. | Cross-sectional |
| Chiappelli et al. (50) | 2014 | 98 with schizophrenia (67% male, 33% female) and 117 control (43% male, 57% female) | Local community mental health clinics. | Maryland Trait and State Depression - scale | BNSS | 36 were taking antidepressants, 15 were taking mood stabilisers | State and trait aspects of Dx and Nx can be separated in schizophrenia. In the schizophrenia sample, Nx and Dx did not correlate. | Cross-sectional - Factor analysis |
| Rossi et al. (51) | 2017 | 921 schizophrenia | outpatients | CDSS | BNSS | Unknown | High negative symptoms predict depression | Cross-sectional |

Beck Depression Inventory (BDI); Hamilton Depression Rating Scale (HDRS); Clinical Global Impression Severity Scale (CGI-S); Scale for the Assessment of Negative Symptoms (SANS); Extrapyramidal Rating Scale (EPRS); Brief Psychiatric Rating Scale (BPRS); Barnes Akathisia Rating Scale (BARS); Significant Others Scale (SOS); Brief Negative Symptoms Scale (BNSS); Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS); Schedule for Affective Disorders and Schizophrenia (SADS); Negative Symptom Rating Scale (NSRS); The Positive and Negative Syndrome Scale (PANSS); Structured Interview for Prodromal Symptoms (SIPS); Scale of Prodromal Symptoms (SOPS); Global Assessment of Functioning (GAF); Scale for the Assessment of

Positive Symptoms (SAPS); Subjective Experience of Negative Symptoms (SENS); Toronto Alexithymia Scale (TAS); SUMD; Extrapyrarnidal Symptom Rating Scale (ESRS); Bech-Rafaelsen Melancholia Scale (BREMS); Calgary Depression Scale in Schizophrenia (CDSS); Abnormal Involuntary Movement Scale (AIMS); Operational Criteria Checklist [OPCRIT]; Multiscore Depression Inventory (MDI); Schedule for Clinical Assessment in Neuropsychiatry (SCAN); Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS); Thought, Language and Communication (TLC).

Table 1: Studies included in the systematic review: characteristics and conclusions (Dx = depression/depressive symptoms; Nx = negative symptoms; Px = positive symptoms)

RESULTS

2210 articles were identified. Following the removal of 892 duplicates, the titles and abstracts of the remaining 1320 articles were screened, and 75 were found to be potentially relevant. Of those 75 papers, read in full, 25 papers met the inclusion criteria and were eligible for the review. References cited in the papers were hand searched, which yielded two further eligible articles, bringing the total number of studies included to 27 (see Figure 1).

Study characteristics

Sampling

Thirteen papers reported on samples from inpatient units (16, 29, 32-34, 36-38, 41, 42, 44, 46, 47) while nine of the studies examined patients in community settings (15, 28, 30, 39, 40, 48-51). One study (22) included participants from both inpatient and outpatient units while the remaining four studies did not provide information on the source of the patient sample (31, 43, 45, 52). The study sample sizes ranged from 42 to 921 participants, with a total number of 3062.

Rating scales used

Depression scales

The majority of studies employed a single scale to assess symptoms of depression, with the most commonly used being either the Hamilton Rating Scale for

Depression (16, 22, 28, 33, 36-38, 40, 41, 52). Six studies used the Calgary Depression Scale for Schizophrenia (CDSS) (15, 42, 45, 48, 49, 51), and Five studies used the Beck Depression Inventory (22, 29, 30, 40).

Negative symptom scales

The majority of studies used either Scale for the Assessment of Negative Symptoms (SANS) (8) or the negative subscale of the Positive and Negative Syndrome Scale (PANSS) (53) to assess negative symptoms; (15, 16, 22, 28-31, 34, 36-45, 48, 49, 52). Five studies (31, 33, 39, 41, 51) used the negative subscale of the Brief Psychiatric Rating Scale (BPRS) (54). Romney et al. (22) rated anhedonia separately using Physical Anhedonia Scale (PAS) (55) and Social Anhedonia Scale (SAS) (56).

Study design and analysis

The majority of studies employed a cross-sectional design (22, 28-31, 34, 36, 39, 40, 42, 45-51). One study adopted a prospective design (16). One study employed a combined prospective and retrospective study design (15) and four studies implemented a prospective, longitudinal study design (32, 37-39). One study reported on a cross-sectional and longitudinal arm (44). An experimental design was used by two studies included in the review; Oosthuizen et al. (43) carried out an open-labelled trial and Tapp et al. (41) conducted a double-blind experiment. Newcomer et al. (33) used a retrospectively-drawn sample. In two studies (22, 50), a factor analysis was included as part of the data analysis.

Medication

Five of the 27 studies reviewed recorded the use of antidepressants, with the prevalence of antidepressant use ranging from 3 to 14% (16, 42, 43, 50, 57). Fourteen reported antipsychotic use (15, 16, 22, 32, 37-39, 41-43, 48-50, 52). Majadas et al. (49) excluded patients who were taking antidepressant medication, while Newcomer et al. (33) sampled patients who were medication naïve. Tharyan et al. (52) sampled both medicated and unmedicated patients.

Prevalence and reporting of negative symptoms and depression

The prevalence of depression in the studies reviewed ranged from 30% to 80%, depending on the criteria for the presence of depression (46, 52) or depressive symptoms (15, 16, 39, 41, 43, 45, 47, 49) that were used.

Factor analysis was reported by 2 studies, which described a depression domain independent from negative symptoms and positive symptoms (22, 50). Symptoms such as low mood, pessimism, suicidal ideation and impaired tolerance to stress were considered depressive features (31, 34). The negative symptom domain included alogia, poor attention and concentration, blunted affect and social withdrawal (28). Anhedonia, emotional blunting, anergia, amotivation, asociality and avolition occurred in both the negative and depressive domains (22, 28, 36).

Results from all of the studies reviewed were tabulated into symptoms that were reported as distinct depressive features, symptoms that were distinct negative symptoms and symptoms that overlapped between the two symptom domains (see Table 2).

| Symptom | Depressive symptoms | Depressive and negative symptoms | Negative symptoms |
|----------------------------------|---------------------|----------------------------------|-------------------|
| Anhedonia | | X | |
| Emotional blunting | | X | |
| Anergia | | X | |
| Amotivation | | X | |
| Asociality | | X | |
| Avolition | | X | |
| Low mood | X | | |
| Pessimism | X | | |
| Suicidal ideation | X | | |
| Observed sadness | | | X |
| Alogia | | | X |
| Poor attention and concentration | | | X |
| Blunted affect | | | X |
| Social withdrawal | | | X |

Table 2: Association of symptoms within the depressive and negative symptoms domains

DISCUSSION

The findings of the studies reviewed suggest whilst considerable heterogeneity is present, some depressive features such as low mood, suicidal ideation, pessimism are distinct from a negative symptom domain characterised by alogia and blunted affect in schizophrenia. For example Liemburg et al. (10) and Messinger et al. (9) found that while depressed mood and suicidal intent reflect a depressive domain, blunted affect and alogia belong to the ‘expressive deficit’ negative symptom domain. Symptoms such as avolition, anergia and amotivation, considered to constitute ‘social amotivation’, appear to occur in both the depressive and negative domains. The findings presented are consistent with those of Whiteford et al. (28), who emphasised that while symptoms such as alogia and poor attention were distinctly negative symptoms, loss of energy and anhedonia were present in both the depressive and negative domains. Observed sadness together with inability to feel was reported as a negative symptom by

Kibel et al. in (1993) (34) as distinguished from subjective sadness. However, this was not replicated by other studies. One explanation for this finding is that there can be a misattribution of blunted affect or lack of facial expression as observed sadness.

Sax et al. (36), found the co-occurrence of depressive and negative symptoms to be confined to poor motivation, anhedonia and social withdrawal, but this may be artefactual; specifically the product of similarly worded items on different rating scales. The findings relating to whether anhedonia should be considered as part of the negative symptom or depressive symptom domains are inconsistent, and our results suggest anhedonia occurs in both. Evidence from factor analysis studies suggests that anhedonia may be more closely aligned with depression rather than schizophrenia (22, 45). Alternatively, it has been considered as a negative symptom of schizophrenia because of its close relationship with blunted affect, emotional blunting and social withdrawal (22).

The inconsistency of classification of anhedonia may partly reflect that anhedonia may be a feature of negative and depressive domains in schizophrenia in different forms, differentiated by distinguishing between anticipatory and consummatory anhedonia. Thus, anhedonia as part of depression may reflect a loss of interest in previously rewarding or enjoyable activity because of the inability to experience pleasure. However, individuals with schizophrenia may experience normal levels of pleasure when engaging in enjoyable activities (consummatory pleasure) but lack the ability to experience pleasure for future activities (anticipatory pleasure), and therefore have an anticipatory anhedonia but not a consummatory anhedonia (58). These may reflect differing underlying processes; abnormal psychological and dysfunctional behavioural processes that are responsible for differing manifestations of

anhedonia (59). However, when Li et al. (60) observed people with moderate depressive disorder and individuals with schizophrenia, they found anticipatory and consummatory anhedonia were present in both conditions. Furthermore, Buck et al. (61) observed strong correlations between scores of consummatory and anticipatory anhedonia in schizophrenia, suggesting that the explanatory value of this distinction regarding anhedonia as a negative or depressive symptom may be limited (61). However, the notion that anhedonia as a negative symptom has a different pathophysiology from its presentation as a depressive symptom is speculative and further research is needed to address this. Furthermore, the findings prompting such a notion may simply reflect a limitation in the scales used to assess the change of hedonic experiences in patients with schizophrenia.

A dimensional model within domains

If we consider negative symptoms as being formed of a diminished-expression domain and avolition-amotivation sub-domain (9), the presented findings suggest that the relationship is primarily between depression and avolition-amotivation phenomena. The relationship between depressive and negative symptoms may be represented in a dimensional model (see figure 2), with symptoms denoting general, attenuated non-specific symptoms; those that span both depressive and negative symptoms (such as anergia and poverty in speech) and those that represent specific symptoms of depression (such as consummatory anhedonia, hopelessness) and negative symptoms (such as anticipatory anhedonia, blunted affect). Levels within a dimensional hierarchy have often been implied in a positive domain e.g. social anxiety/subtle self-referential

thinking building to brief attenuated symptoms followed by frank delusional beliefs and hallucinations (see Mishara et al. (62).

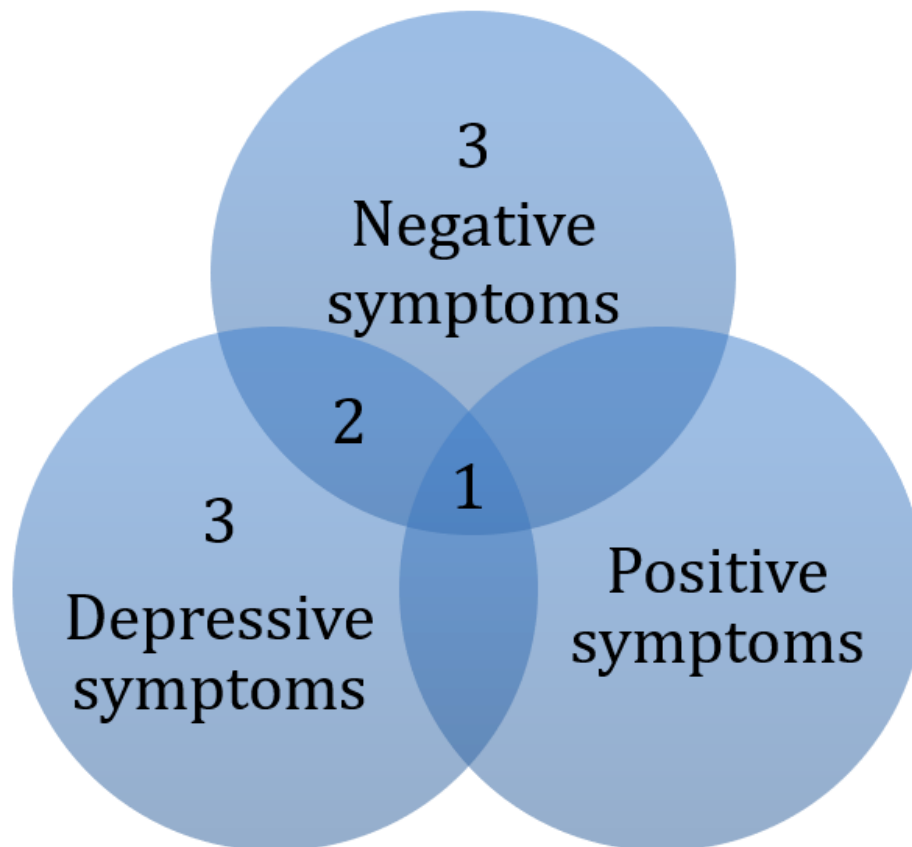


Figure 2. Dimensional model of negative, depressive and positive symptoms in schizophrenia. 1= General, attenuated non-specific symptoms; 2. Symptoms that span both depressive and negative symptoms; and 3. Symptoms specific to the depressive or negative symptoms domains

In our model, symptoms that form the expressive deficits sub-domain appear to be specific to negative symptoms, and are represented by '3' in the negative symptom domain of our dimensional model. Symptoms such as low mood, suicidal ideation and pessimism are considered core features of depression and are denoted by '3' in the depression domain. Symptoms that form the avolition-amotivation subdomain of

negative symptoms appear to consist of features that span both depressive and negative syndromes, and are represented by '2' in our dimensional model.

However only one of the studies (50) employed a scale that allows for the distinction between the two negative symptom sub-domains (the Brief Negative Symptom Scale) (63). This highlights the importance of future studies using scales able to assess the distinction between the sub-domains that form negative symptoms, such as the Clinical Assessment Interview for Negative Symptoms (CAINS: (64). This would have particular implications for studies assessing the effectiveness of domain specific interventions.

Limitations

Studies included were markedly heterogeneous; both medicated and unmedicated patients were included in the study samples as well as broad diagnostic groups including schizophrenia and first-episode psychosis. There was also a lack of consistency regarding the methods used to assess depression and negative symptoms. It can be argued that the SANS (8) provides the most comprehensive and valid coverage of negative symptom domains in schizophrenia and is highly tuned to detecting differences between positive and negative symptoms in schizophrenia, yet it was not universally used. However, the use of the SANS has its limitations not least the item assessing attention, which may be considered a manifestation of cognitive dysfunction and not form part of the negative syndrome. Nevertheless, no phenomenological measure has been developed is able to differentiate between primary and secondary negative symptoms, and the subjective experiences related to negative symptoms are

not elicited (65-67). Also, to measure depression, some studies used the HRSD (22), others used the CDSS (15) and some others used the BDI (40).

Implications

The DSM RDoC criteria and NIMH objectives recommend that research studies should focus increasingly on specific indicative symptoms to ascertain treatment effects (68, 69). Our review has suggested a putative model (see Figure 2) which could be used as a starting point for the investigation underlying biological processes and targeted treatment within a dimensional psychosis model (70-72). Being able to clinically distinguish between depressive and negative symptoms in schizophrenia would not only allow for early, targeted treatment, but may also provide some indication of a patient's symptom burden and possibly have implications for prognosis, which can then be used to help inform a tailored treatment plan. Discriminating between anticipatory and consummatory anhedonia may prove to be a useful distinction in relation to association with either the depressive or negative domain which would suggest that the two domains within anhedonia (consummatory and anticipatory) may be products of differing aetiology.

Distinguishing between these two domains may provide clinical benefit through targeted therapy, which can be directed at either anticipatory or consummatory anhedonia and has been shown to be effective when applying psychological therapy (73). To date, there have been relatively few studies assessing the use of antidepressants to treat depression in schizophrenia and those that have been reported yielded mixed results, possibly the result of poor understanding of the core symptoms

of depression therein (74-78) Furthermore, to understand the relationship between depression and negative symptoms in schizophrenia, highly sensitive measures and thorough longitudinal studies, which chart symptom development and course, are required.

References

1. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry*. 2013;70(10):1107-12.
2. Murray V, McKee I, Miller PM, Young D, Muir WJ, Pelosi AJ, et al. Dimensions and classes of psychosis in a population cohort: a four-class, four-dimension model of schizophrenia and affective psychoses. *Psychological Medicine*. 2005;35(04):499-510.
3. Upthegrove R, Marwaha S, Birchwood M. Depression and Schizophrenia: Cause, Consequence or Trans-diagnostic Issue? *Schizophrenia Bulletin*. 2016.
4. Craddock N, Owen MJ. The Kraepelinian dichotomy – going, going... but still not gone. *The British Journal of Psychiatry*. 2010;196(2):92-5.
5. Koutsouleris N, Meisenzahl EM, Borgwardt S, Riecher-Rössler A, Frodl T, Kambitz J, et al. Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. *Brain*. 2015;138(Pt 7):2059-73.
6. Barnes. Clinical assessment of the negative symptoms of schizophrenia. *European Neuropsychopharmacology*. 1993;3:207-8.
7. Malla AK. Negative symptoms and affective disturbance in schizophrenia and related disorders. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 1995;40(7 Suppl 2):S55-9.
8. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry*. 1982;39(7):784-8.
9. Messinger JW, Trémeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, et al. Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical psychology review*. 2011;31(1):161-8.

10. Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *J Psychiatr Res.* 2013;47(6):718-25.
11. Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *Eur Neuropsychopharmacol.* 2014;24(5):693-709.
12. Kaiser S, Heekeren K, Simon JJ. The negative symptoms of schizophrenia: category or continuum? *Psychopathology.* 2011;44(6):345-53.
13. Kaiser S, Lyne J, Agartz I, Clarke M, Morch-Johnsen L, Faerden A. Individual negative symptoms and domains - Relevance for assessment, pathomechanisms and treatment. *Schizophrenia research.* 2016.
14. Beck AT. *Depression: Clinical, Experimental, and Theoretical Aspects.* Philadelphia University of Philadelphia Press; 1967.
15. Uptegrove, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatr Scand.* 2010;122(3):211-8.
16. Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. *American Journal of Psychiatry.* 1993;150(11):1643-8.
17. Siris SG, Adan F, Cohen M, Mandeli J, Aronson A, Casey E. Postpsychotic depression and negative symptoms: an investigation of syndromal overlap. *American Journal of Psychiatry.* 1988;145(12):1532-7.
18. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophrenia research.* 1990;3(4):247-51.
19. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. *Arch Gen Psychiatry.* 1982;39(7):789-94.
20. Carpenter WT, Jr., Heinrichs DW, Alphas LD. Treatment of negative symptoms. *Schizophrenia Bulletin.* 1985;11(3):440-52.
21. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? *Br Med J.* 1980;280(6207):66-8.
22. Romney DM, Candido CL. Anhedonia in depression and schizophrenia: A reexamination. *Journal of Nervous and Mental Disease.* 2001;189(11):735-40.
23. Lindenmayer J-P, Kay R. Depression, affect and negative symptoms in schizophrenia. *The British Journal of Psychiatry.* 1989;155(Suppl 7):108-14.
24. Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *The British Journal of Psychiatry.* 1987;151(2):145-51.

25. van Os J. Dimensional classification of schizophrenia. *Schizophrenia research*. 2008;102(1-3, Supplement 2):45-.
26. Conley RR, Ascher-Svanum H, Zhu B, Faries D, Kinon BJ. The Burden of Depressive Symptoms in the Long-Term Treatment of Patients With Schizophrenia. *Schizophrenia research*. 2007;90(1-3):186-97.
27. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339.
28. Whiteford A, Riney J, Csernansky G. Distinguishing depressive and negative symptoms in chronic schizophrenia. *Psychopathology*. 1987;20(5):234-6.
29. Barnes T, Curson A, Liddle F, Patel M. The nature and prevalence of depression in chronic schizophrenic in-patients. *The British Journal of Psychiatry*. 1989;154():486-91.
30. Pogue-Geile M. Negative symptoms and depression in schizophrenia. *Depression in schizophrenics*. 1989:121-30.
31. Kulhara P, Avasthi A, Chadda R, Chandiramani K, Mattoo SK, Kota SK, et al. Negative and depressive symptoms in schizophrenia. *The British Journal of Psychiatry*. 1989;154:207-11.
32. Ragin AB, Pogue-Geile M, Oltmanns TF. Poverty of speech in schizophrenia and depression during in-patient and post-hospital periods. *British Journal of Psychiatry*. 1989;154:52-7.
33. Newcomer W, Faustman O, Yeh W, Csernansky G. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. *Psychiatry Research*. 1990;31(3):243-50.
34. Kibel DA, Laffont I, Liddle PF. The composition of the negative syndrome of chronic schizophrenia. *British Journal of Psychiatry*. 1993;162:744-50.
35. Tharyan A, Kuruvilla K. The correlates of the syndrome of depression in schizophrenia. *Indian Journal of Psychiatry*. 1994;36(2):74-8.
36. Sax KW, Strakowski SM, Keck PE, Jr., Upadhyaya VH, West SA, McElroy SL. Relationships among negative, positive, and depressive symptoms in schizophrenia and psychotic depression. *British Journal of Psychiatry*. 1996;168(1):68-71.
37. Nakaya M, Ohmori K, Komahashi T, Suwa H. Depressive symptoms in acute schizophrenic inpatients. *Schizophrenia research*. 1997;25(2):131-9.
38. Nakaya M, Komahashi T, Ohmori K, Suwa H. The composition of the depressive syndrome in acute schizophrenia. *Schizophrenia research*. 1998;34(3):151-7.

39. Zisook S, McAdams LA, Kuck J, Harris MJ, Bailey A, Patterson L, et al. Depressive symptoms in schizophrenia. *The American journal of psychiatry*. 1999;156(11):1736-43.
40. Baynes D, Mulholland C, Cooper SJ, Montgomery RC, MacFlynn G, Lynch G, et al. Depressive symptoms in stable chronic schizophrenia: Prevalence and relationship to psychopathology and treatment. *Schizophrenia research*. 2000;45(1-2):47-56.
41. Tapp A, Kilzieh N, Wood AE, Raskind M, Tandon R. Depression in patients with schizophrenia during an acute psychotic episode. *Comprehensive Psychiatry*. 2001;42(4):314-8.
42. Muller. MJ, Kienzle B, Dahmen N. Depression, emotional blunting, and akinesia in schizophrenia: Overlap and differentiation. *European Journal of Health Economics*. 2002;3(SUPPL. 2):S99-S103.
43. Oosthuizen P, Emsley RA, Roberts MC, Turner J, Keyter L, Keyter N, et al. Depressive symptoms at baseline predict fewer negative symptoms at follow-up in patients with first-episode schizophrenia. *Schizophrenia research*. 2002;58(2-3):247-52.
44. Bottlender R, Sato T, Groll C, Jager M, Kunze I, Moller HJ. Negative symptoms in depressed and schizophrenic patients: How do they differ? *Journal of Clinical Psychiatry*. 2003;64(8):954-8.
45. Maggini C, Raballo A, Salvatore P. Depressive and basic symptoms in schizophrenia. *Neurology Psychiatry and Brain Research*. 2004;11(1):1-6.
46. Hafner H, Maurer K, Trendler G, An WH, Schmidt M. The early course of schizophrenia and depression. *European Archives of Psychiatry and Clinical Neuroscience*. 2005;255(3):167-73.
47. Hafner H, Maurer K, Trendler G, An WH, Schmidt M, Konnecke R. Schizophrenia and depression: Challenging the paradigm of two separate diseases - A controlled study of schizophrenia, depression and healthy controls. *Schizophrenia research*. 2005;77(1):11-24.
48. Rocca P, Bellino S, Calvarese P, Marchiaro L, Patria L, Rasetti R, et al. Depressive and negative symptoms in schizophrenia: Different effects on clinical features. *Comprehensive Psychiatry*. 2005;46(4):304-10.
49. Majadas S, Olivares J, Galan J, Diez T. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. *Comprehensive Psychiatry*. 2012;53(2):145-51.
50. Chiappelli J, Nugent KL, Thangavelu K, Searcy K, Hong LE. Assessment of trait and state aspects of depression in schizophrenia. *Schizophrenia Bulletin*. 2014;40(1):132-42.

51. Rossi A, Stratta P, Galderisi S, Bucci P, Mucci A, Maj M, et al. Personal resources and depression in schizophrenia: The role of self-esteem, resilience and internalized stigma. *Psychiatry Research*. 2017;256:359-64.
52. Tharyan A, Kuruvilla K. The correlates of the syndrome of depression in schizophrenia. *Indian journal of psychiatry*. 1994;36(2):74-8.
53. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-76.
54. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Reports*. 1962;10(3):799-812.
55. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. . *J Abnorm Psychol*. 1976;85:374-82.
56. Eckblad ML, Chapman LJ, Chapman JP, Mishlove M. Revised social anhedonia scale. *J Abnorm Psychol*. 1982;94:384-96.
57. Muller M, Szegedi A, Wetzel H, Benkert O. Depressive factors and their relationships with other symptom domains in schizophrenia, schizoaffective disorder, and psychotic depression. *Schizophrenia Bulletin*. 2001;27(1):19-28.
58. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophrenia research*. 2007;93(1-3):253-60.
59. Dowd EC, Barch DM. Anhedonia and Emotional Experience in Schizophrenia: Neural and Behavioral Indicators. *Biological psychiatry*. 2010;67(10):902-11.
60. Li Y, Mou X, Jiang W, Yang Z, Shen X, Jin Z, et al. A comparative study of anhedonia components between major depression and schizophrenia in Chinese populations. *Annals of General Psychiatry*. 2015;14:24.
61. Buck B, Lysaker PH. Consummatory and anticipatory anhedonia in schizophrenia: stability, and associations with emotional distress and social function over six months. *Psychiatry Res*. 2013;205(1-2):30-5.
62. Mishara AL, Fusar-Poli P. The Phenomenology and Neurobiology of Delusion Formation During Psychosis Onset: Jaspers, Truman Symptoms, and Aberrant Salience. *Schizophrenia Bulletin*. 2013;39(2):278-86.
63. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull*. 2011;37(2):300-5.
64. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): Final Development and Validation. *The American journal of psychiatry*. 2013;170(2):165-72.

65. Lincoln TM, Dollfus S, Lyne J. Current developments and challenges in the assessment of negative symptoms. *Schizophrenia research*. 2016.
66. Liddle PF, Barnes TRE, Curson DA, Patel M. Depression and the experience of psychological deficits in schizophrenia. *Acta Psychiatrica Scandinavica*. 1993;88(4):243-7.
67. Liddle PF, Barnes TRE. The Subjective Experience of Deficits in Schizophrenia. *Comprehensive Psychiatry*. 1988;29:157-64.
68. Whitehead C, Moss S, Cardno A, Lewis G. Antidepressants for people with both schizophrenia and depression. *Cochrane database of systematic reviews (Online)*. 2002(2):CD002305.
69. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010;167(7):748-51.
70. Noto C, Ota VK, Santoro ML, Ortiz BB, Rizzo LB, Higuchi CH, et al. Effects of depression on the cytokine profile in drug naive first-episode psychosis. *Schizophrenia research*. 2015;164(1-3):53-8.
71. Kumari V, Peters E, Guinn A, Fannon D, Russell T, Sumich A, et al. Mapping Depression in Schizophrenia: A Functional Magnetic Resonance Imaging Study. *Schizophrenia Bulletin*. 2016;42(3):802-13.
72. Chuang JY, Murray GK, Metastasio A, Segarra N, Tait R, Spencer J, et al. Brain structural signatures of negative symptoms in depression and schizophrenia. *Front Psychiatry*. 2014;5:116.
73. Favrod J, Giuliani F, Ernst F, Bonsack C. Anticipatory Pleasure Skills Training: A New Intervention to Reduce Anhedonia in Schizophrenia. *Perspectives in Psychiatric Care*. 2010;46(3):171-81.
74. Goode DJ, Manning AA. Comparison of bupropion alone and with haloperidol in schizo-affective disorder, depressed type. *J Clin Psychiatry*. 1983;44(7):253-5.
75. Kirli S, Caliskan M. A comparative study of sertraline versus imipramine in postpsychotic depressive disorder of schizophrenia. *Schizophrenia research*. 1998;33(1-2):103-11.
76. Mulholland C, Lynch G, King DJ, Cooper SJ. A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. *J Psychopharmacol*. 2003;17(1):107-12.
77. Sandhu A, Ives J, Birchwood M, Uptegrove R. The subjective experience and phenomenology of depression following first episode psychosis: A qualitative study using photo-elicitation. *Journal of Affective Disorders*. 2013;149(1):166-74.

78. Barnes TRE, Leeson VC, Paton C, Costelloe C, Simon J, Kiss N, et al. Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS): a double-blind, placebo-controlled, randomised clinical trial. *Health Technol Assess.* 2016;20(29).

Supplementary table 1
Search strategy for systematic review

| | Database(s) | Search Term |
|-----------------------------|-------------|--|
| <input type="checkbox"/> 1 | Medline | exp SCHIZOPHRENIA/ OR SCHIZOPHRENIA, CATATONIC/ OR SCHIZOPHRENIA, CHILDHOOD/ OR SCHIZOPHRENIA, DISORGANIZED/ OR SCHIZOPHRENIA, PARANOID/ |
| <input type="checkbox"/> 2 | Medline | PSYCHOTIC DISORDERS/ |
| <input type="checkbox"/> 3 | Medline | (schizophren* OR psychosis OR psychoses OR FEP).ti |
| <input type="checkbox"/> 4 | Medline | <i>(1 OR 2 OR 3)</i> |
| <input type="checkbox"/> 5 | Medline | exp DEPRESSION/ |
| <input type="checkbox"/> 6 | Medline | (depres*).ti |
| <input type="checkbox"/> 7 | Medline | DEPRESSIVE DISORDER/ |
| <input type="checkbox"/> 8 | Medline | DYSTHYMIC DISORDER/ OR DEPRESSIVE DISORDER, MAJOR/ |
| <input type="checkbox"/> 9 | Medline | <i>(5 OR 6 OR 7 OR 8)</i> |
| <input type="checkbox"/> 10 | Medline | ANHEDONIA/ |
| <input type="checkbox"/> 11 | Medline | APATHY/ |
| <input type="checkbox"/> 12 | Medline | (alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab |
| <input type="checkbox"/> 13 | Medline | ("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab |
| <input type="checkbox"/> 14 | Medline | ("NEGATIVE SYMPTOM*").ti,ab |
| <input type="checkbox"/> 15 | Medline | <i>(10 OR 11 OR 12 OR 13 OR 14)</i> |
| <input type="checkbox"/> 16 | Medline | <i>(4 AND 9 AND 15)</i> |
| <input type="checkbox"/> 17 | Medline | <i>16 [DT 2014-2017] [Languages English]</i> |
| <input type="checkbox"/> 18 | PsycINFO | exp SCHIZOPHRENIA/ |
| <input type="checkbox"/> 19 | PsycINFO | PSYCHOSIS/ |
| <input type="checkbox"/> 20 | PsycINFO | (schizophren* OR psychosis OR psychoses OR FEP).ti |
| <input type="checkbox"/> 21 | PsycINFO | <i>(18 OR 19 OR 20)</i> |
| <input type="checkbox"/> 22 | PsycINFO | MAJOR DEPRESSION/ OR RECURRENT DEPRESSION/ OR TREATMENT RESISTANT DEPRESSION/ |
| <input type="checkbox"/> 23 | PsycINFO | DYSTHYMIC DISORDER/ |
| <input type="checkbox"/> 24 | PsycINFO | (depres*).ti |

| | | |
|-----------------------------|----------|---|
| <input type="checkbox"/> 25 | PsycINFO | <i>(22 OR 23 OR 24)</i> |
| <input type="checkbox"/> 26 | PsycINFO | POSITIVE AND NEGATIVE SYMPTOMS/ |
| <input type="checkbox"/> 27 | PsycINFO | ANHEDONIA/ |
| <input type="checkbox"/> 28 | PsycINFO | APATHY/ |
| <input type="checkbox"/> 29 | PsycINFO | (alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab |
| <input type="checkbox"/> 30 | PsycINFO | ("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab |
| <input type="checkbox"/> 31 | PsycINFO | ("NEGATIVE SYMPTOM*").ti,ab |
| <input type="checkbox"/> 32 | PsycINFO | <i>(26 OR 27 OR 28 OR 29 OR 30 OR 31)</i> |
| <input type="checkbox"/> 33 | PsycINFO | <i>(21 AND 25 AND 32)</i> |
| <input type="checkbox"/> 34 | PsycINFO | <i>33 [DT 2014-2017] [Languages English]</i> |
| <input type="checkbox"/> 35 | EMBASE | *SCHIZOPHRENIA/ OR *PARANOID SCHIZOPHRENIA/ OR *PSYCHOSIS/ |
| <input type="checkbox"/> 36 | EMBASE | (schizophren* OR psychosis OR psychoses OR FEP).ti |
| <input type="checkbox"/> 37 | EMBASE | <i>(35 OR 36)</i> |
| <input type="checkbox"/> 38 | EMBASE | *DEPRESSION/ OR *MAJOR DEPRESSION/ |
| <input type="checkbox"/> 39 | EMBASE | *DYSTHYMIA/ |
| <input type="checkbox"/> 40 | EMBASE | (depres*).ti |
| <input type="checkbox"/> 41 | EMBASE | <i>(38 OR 39 OR 40)</i> |
| <input type="checkbox"/> 42 | EMBASE | *BLUNTED AFFECT/ OR *ANHEDONIA/ OR *APATHY/ OR *NEGATIVE SYNDROME/ |
| <input type="checkbox"/> 43 | EMBASE | ("negative symptom*").ti,ab |
| <input type="checkbox"/> 44 | EMBASE | (alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab |
| <input type="checkbox"/> 45 | EMBASE | ("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab |
| <input type="checkbox"/> 46 | EMBASE | <i>(42 OR 43 OR 44 OR 45)</i> |
| <input type="checkbox"/> 47 | EMBASE | <i>(37 AND 41 AND 46)</i> |
| <input type="checkbox"/> 48 | EMBASE | <i>47 [DT 2014-2017] [Languages English]</i> |
| <input type="checkbox"/> 49 | Medline | "MOOD DISORDERS" / |
| <input type="checkbox"/> 50 | Medline | ("mood disorder*").ti |

| | | | |
|--------------------------|----|----------|---------------------------|
| <input type="checkbox"/> | 51 | Medline | <i>(49 OR 50)</i> |
| <input type="checkbox"/> | 52 | Medline | <i>(4 AND 15 AND 51)</i> |
| <input type="checkbox"/> | 53 | Medline | <i>(9 OR 51)</i> |
| <input type="checkbox"/> | 54 | Medline | <i>(4 AND 15 AND 53)</i> |
| <input type="checkbox"/> | 55 | Medline | <i>54 [DT 2017-2018]</i> |
| <input type="checkbox"/> | 56 | PsycINFO | "AFFECTIVE DISORDERS"/ |
| <input type="checkbox"/> | 57 | PsycINFO | ("mood disorder*").ti |
| <input type="checkbox"/> | 58 | PsycINFO | <i>(56 OR 57)</i> |
| <input type="checkbox"/> | 59 | PsycINFO | <i>(21 AND 32 AND 58)</i> |
| <input type="checkbox"/> | 60 | PsycINFO | <i>(25 OR 59)</i> |
| <input type="checkbox"/> | 61 | PsycINFO | <i>(21 AND 32 AND 60)</i> |
| <input type="checkbox"/> | 62 | PsycINFO | <i>61 [DT 2017-2018]</i> |
| <input type="checkbox"/> | 63 | EMBASE | *"MOOD DISORDER"/ |
| <input type="checkbox"/> | 64 | EMBASE | ("mood disorder*").ti |
| <input type="checkbox"/> | 65 | EMBASE | <i>(63 OR 64)</i> |
| <input type="checkbox"/> | 66 | EMBASE | <i>(37 AND 46 AND 65)</i> |
| <input type="checkbox"/> | 67 | EMBASE | <i>(41 OR 65)</i> |
| <input type="checkbox"/> | 68 | EMBASE | <i>(37 AND 46 AND 67)</i> |
| <input type="checkbox"/> | 69 | EMBASE | <i>68 [DT 2017-2018]</i> |

| | | | |
|--------------------------|----|----------|--|
| <input type="checkbox"/> | 86 | EMBASE | *SCHIZOAFFECTIVE PSYCHOSIS/ |
| <input type="checkbox"/> | 87 | EMBASE | 81 AND 86 [Limit to: English Language] |
| <input type="checkbox"/> | 88 | EMBASE | *AFFECTIVE PSYCHOSIS/ |
| <input type="checkbox"/> | 89 | EMBASE | 86 OR 88 |
| <input type="checkbox"/> | 90 | EMBASE | 81 AND 89 [Limit to: English Language] |
| <input type="checkbox"/> | 91 | PsycINFO | SCHIZOAFFECTIVE DISORDER/ |
| <input type="checkbox"/> | 92 | PsycINFO | 55 AND 91 [Limit to: English Language] |
| <input type="checkbox"/> | 93 | MEDLINE | SCHIZOAFFECTIVE DISORDER/ |
| <input type="checkbox"/> | 95 | MEDLINE | AFFECTIVE DISORDERS, PSYCHOTIC/ |
| <input type="checkbox"/> | 96 | MEDLINE | 93 OR 95 |
| <input type="checkbox"/> | 97 | MEDLINE | 23 AND 96 [Limit to: English Language] |

