Patient Related Outcome Measures

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REVIEW

Systematic Literature Review of Studies Reporting Measures of Functional Outcome or Quality of Life in People with Negative Symptoms of Schizophrenia

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Aim: Negative symptoms of schizophrenia (NSS) have been linked with poor functional outcomes. A literature review was performed to identify instruments used to assess functional outcomes and quality of life in clinical trials and observational studies conducted in groups of people with NSS.

Methods: Literature search strings were designed using Medical Subject Headings combined with free-text terms and searches were performed using the PubMed, Embase and the Cochrane Library databases. For inclusion, articles were required to be published as full-text articles, in English, over the period 2011–2021, include at least one group or treatment arm of people with NSS and report either functional outcomes or quality of life (QoL).

Results: Literature searches identified a total of 3,268 unique hits. After two rounds of screening, 37 publications (covering 35 individual studies) were included in the review. A total of fourteen different instruments were used to assess functional outcomes and eleven different instruments were used to assess QoL. In studies in people with NSS, the most frequently used functional outcome measures were the Personal and Social Performance scale and the Global Assessment of Functioning. The most frequently used QoL instruments included the Manchester Short Assessment of Quality of Life, the Heinrich Carpenter Quality of Life Scale, the Schizophrenia Quality of Life Scale and the EQ-5D.

Conclusion: A large number of measures have been used to assess functional outcomes and QoL in people with NSS, these include both generic and condition-specific as well as both interviewer-administered and self-reported instruments.

Keywords: schizophrenia, quality of life, functional outcomes, negative symptoms

Introduction

It is estimated that up to 60% of people with schizophrenia have negative symptoms to an extent that warrants treatment.[1] Negative symptoms of schizophrenia (NSS) include avolition, anhedonia, asociality, affective blunting/flattening and alogia.[2,3] NSS may also be classified as either primary or secondary, with primary NSS being related to the disease process itself, whereas secondary NSS are related to other factors such as the presence of depression, social isolation or deprivation, or side effects of medication.[4] Currently available pharmacologic treatments are effective in terms of reducing the positive symptoms of schizophrenia (eg, hallucinations, delusions); however, NSS typically respond poorly to currently available treatments[3] and the effective management of NSS is acknowledged as an unmet need.[5] The use of measures that can quantify the magnitude and extent of NSS is important in terms of determining the severity of NSS and also in quantifying the treatment effects of interventions targeting NSS; however, there are several factors that may make the measurement of NSS (and treatment effects targeting NSS) challenging. For example, it may be difficult to delineate

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primary versus secondary NSS[1] and there may be potential for inter-observer variability in terms of quantifying NSS, although this may be reduced with training.[6]

NSS can have a detrimental effect on everyday life and have been linked to poor quality of life (QoL) and impaired functional outcomes.[7,8] Functional outcomes include activities of daily living, social relationships and QoL[9] and a greater severity of NSS has been linked with worse functional outcomes.[8] An improvement in functional outcomes is also increasingly recognized as an important metric in terms of recovery.[10]

Several measures are available to assess QoL and functional outcomes, which may be of interest to investigators examining the efficacy of new interventions. These can be either condition-specific or generic measures and can be either self-reported or interviewer-administered, each of which are associated with relative merits and limitations. Given the importance of functional outcomes and the intricate association between NSS and functional outcomes, a literature review was conducted to identify measures that have been used to assess functional outcomes and QoL endpoints in clinical trials and observational studies conducted in people with NSS. The unmet clinical need for efficacious treatments specifically targeting NSS provided part of the rationale for focusing exclusively on studies conducted in people with NSS.

Methods

Literature search strategies were designed using high-level Medical Subject Headings (MeSH) terms combined with free-text terms and searches were run using the PubMed, Embase and Cochrane Library databases in June 2021. Full details of the search strategies for each database are available in the Supplementary Tables 1–3. The timeframe of the searches was limited to the previous 10 years and studies were required to be published in English as full-text articles.

Inclusion/exclusion criteria were developed. Specifically, for inclusion, studies were required to have at least one treatment arm or group of people with NSS (either by stating that patients had NSS or applying a minimum threshold level for NSS on a recognized scale, including but not limited to the Positive and Negative Syndrome Scale [PANSS], Scale for the Assessment of Negative Symptoms [SANS] or the Negative Symptom Assessment 16 [NSA-16]). The focus of the review was on studies where the presence of NSS was a prerequisite for inclusion rather than studies investigating the efficacy/effectiveness of pharmacologic or non-pharmacologic interventions in terms of a reduction in NSS as measured by scales such as the PANSS or SANS. Studies were also required to be conducted exclusively in people with schizophrenia; studies conducted in mixed groups of people with schizophrenia and other affective or non-affective disorders (eg, schizoaffective disorder, bipolar disorder, delusional disorder, etc.) were excluded. For inclusion, studies were also required to report at least one QoL or functional outcome endpoint, either as a primary, secondary or exploratory/ancillary endpoint. No exclusion criteria relating to type of intervention were applied; as such, studies on pharmacologic agents, non-pharmacologic interventions and psychological interventions were eligible for inclusion.

Search results from all three databases were uploaded into the web-based systematic literature review software Sourcerer (https://sourcerer.pro; Covalence Research Ltd, Harpenden, UK). Duplicates were removed and first-round screening of titles and abstracts was performed independently by two reviewers. Full-text second round screening and data extraction of relevant articles were then performed.

Results

Literature searches across all three databases identified a total of 4,297 hits, of which 1,029 were duplicates, resulting in a total of 3,268 unique hits. A total of 3,132 hits were excluded during first-round title and abstract screening and a further 99 were excluded during second-round full-text screening. Consequently, a total of 37 articles, covering 35 individual studies were included in the review (Figure 1).

The studies identified were heterogeneous in terms of the sample group, with a small number of studies (n=3) conducted exclusively in inpatients but the majority were either conducted in outpatients or did not state whether the study group comprised inpatients or outpatients (Table 1). The definitions and threshold levels used to define the presence of negative symptoms were also heterogenous although the most commonly used method was to apply a minimum score on either the PANSS negative subscale (items N1–N7 of the PANSS scale) or the PANSS negative symptom factor (Marder) score (NSFS; items N1, N2, N3, N4, N6, G7 and G16 on the PANSS scale) (Supplementary Table 4). For the PANSS, the

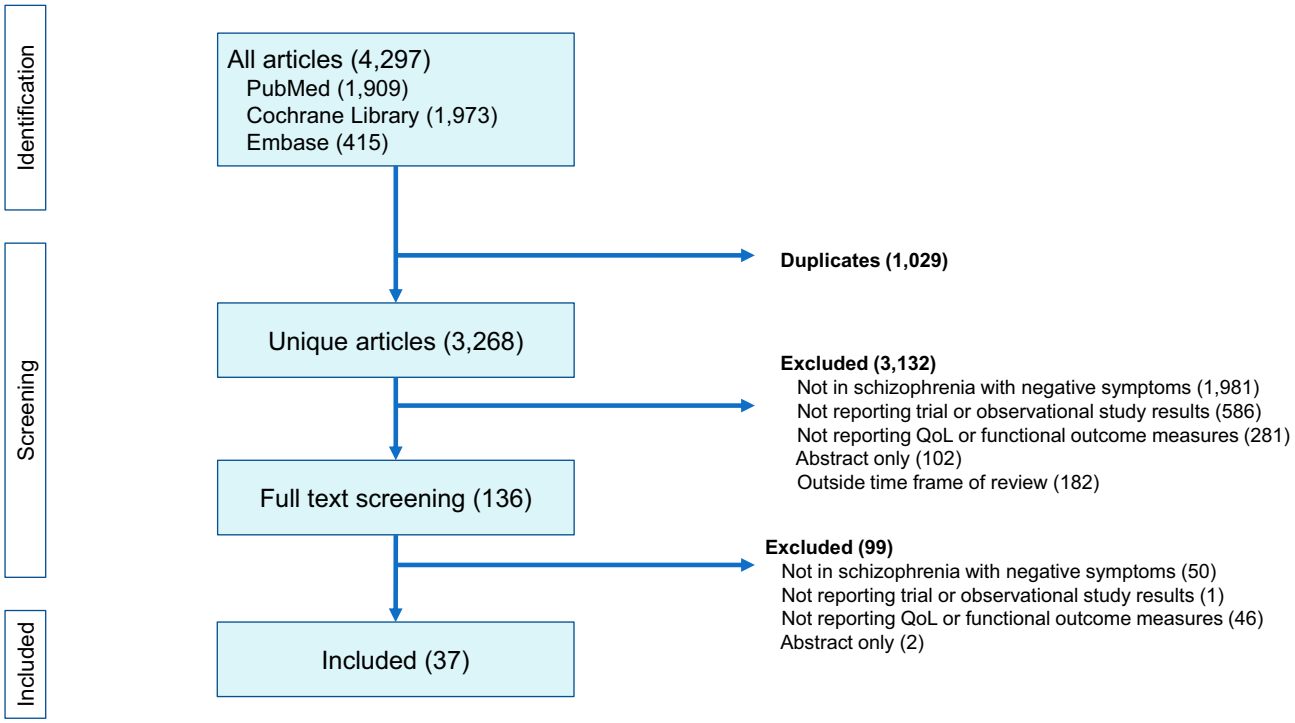

Figure 1 Summary of literature review process.
Note: This figure represents the number of publications not the number of individual studies; some publications included more than one study and some studies were captured in multiple publications. Articles classed as not reporting trial or observational study results included case studies, narrative reviews, protocols, etc. A 10-year time horizon was applied to searches, despite this, multiple articles were excluded during first-round screening owing to publication outside the timeframe of the review.
Abbreviation: QoL, quality of life.

minimum negative symptom scores required for study entry ranged from ≥15[25] to ≥24[19,20] although a score of ≥20 was the most commonly applied threshold using the PANSS negative symptom scores (see Supplementary Table 4). Other criteria used to define NSS included minimum scores on the SANS or Proxy for Deficit Syndrome.

Functional Outcome Assessment Measures

A total of fourteen different functional outcome measures were identified across the included studies (Table 2). A further two studies included functional outcome as an endpoint measure but did not use a specific instrument to assess this. Instead, Novick et al[33] assessed the level of social functioning by quantifying the number of activities performed with friends/social groups in the preceding 4 weeks and Liu et al[31] classified patients as either high or low functioning based on assessment of several factors including personal relationships, family life, achievement and time planning. In the included articles, functional outcome was typically either a secondary or exploratory/ancillary endpoint.

The instruments used to assess functional outcomes included both self-reported and interviewer-administered measures as well as measures specifically designed for use in mental health (eg, the Personal and Social Performance Scale [PSP], Social and Occupational Functioning Assessment Scale [SOFAS] and Global Assessment of Functioning [GAF]) as well as more generic measures of functioning such as the Sheehan Disability Scale (SDS) and the World Health Organization Disability Assessment Scale 2.0 (WHODAS 2.0).

The most frequently used measure was the PSP, which was used in a total of eleven different publications covering ten individual studies.[14–20,24,25,39,44] The PSP was developed from the SOFAS, which was in turn developed from the GAF. The PSP was developed by Morosini et al[48] to improve and overcome some of the limitations of the GAF and is therefore similar in structure to both the SOFAS and the GAF. It is reported to have better face validity relative to the SOFAS.[48] The PSP is an investigator-reported measure (a self-reported version is also available)[49] that takes approximately 5−10 minutes to complete and assesses functioning across four different areas (socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors). The output of the PSP is a single score

Table 1 Summary of Included Publications

Study	Study Number	Patients, n	Inpatient/ Outpatient	Planned Duration of Treatment	Male, %	Mean (SD) age, years	Mean (SD) Duration of Disease, Years	Mean (SD) age at Diagnosis, Years
Beck et al 2013[11] (United States)	NR	94	Outpatient	N/A	75.5	Deficit: 39.9 (11.1) Non-deficit: 39.4 (12.2)	NR	NR
Bryl et al 2020[12] (United States)	NR	31	NR	10 weeks	64.5	Dance/movement therapy: 44.67 (10.97) Treatment as usual: 48.38 (12.70)	Dance/movement therapy: 18.94 (11.36) Treatment as usual: 28.92 (11.08)	NR
Buchanan et al 2012[13] (Multinational)	NCT00212836 NCT00265343 NCT00145496 NCT00174265	949	Mainly outpatient	26 weeks	Eastern Hemisphere: Asenapine: 68 Olanzapine: 68.3 Western Hemisphere: Asenapine: 72.1 Olanzapine: 75.9	Eastern Hemisphere: Asenapine: 40.7 (12.7) Olanzapine: 40.3 (11.7) Western Hemisphere: Asenapine: 43.1 (11.4) Olanzapine: 42.8 (11.3)	NR	Eastern Hemisphere: Asenapine: 27.7 (10.3) Olanzapine: 28.1 (9.4) Western Hemisphere: Asenapine: 24.6 (8.0) Olanzapine: 26.2 (9.3)
Burgarski-Kirola et al 2017[14] (Multinational)	NCT01192906 and NCT01192867	Daylyte n=605 and Flashlyte n=594 (ITT population)	NR	24 weeks	Daylyte: 69.2 Flashlyte: 67.6	Daylyte: Bitopertin 5 mg: 42.0 (11.8) Bitopertin 10 mg: 39.8 (11.3) Placebo: 42.3 (12.0) Flashlyte: Bitopertin 10 mg: 41.1 (11.2) Bitopertin 20 mg: 38.2 (12.0) Placebo: 38.7 (12.3)	NR	NR
Dunayevich et al 2017[15] (Multinational)	NCT01568216 and NCT01568229	232	NR	12 weeks	67.2	43.9 (10.5)	NR	NR

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Edgar et al 2014[16] (Multinational)	NCT00616798	323	Outpatient	NR	64	Median approx. 40	Approx. 11.5	NR
Rofail et al 2016[17] (Multinational)	NCT00616798	312	NR	8 weeks	64.1	39.9 (10.1)	11.6 (9.0)	NR
Umbricht et al 2014[18] (Multinational)	NCT00616798	323	NR	8 weeks	Bitopertin 10 mg: 68 Bitopertin 30 mg: 53 Bitopertin 60 mg: 62 Placebo: 56	Bitopertin 10 mg: 41.1 (10.4) Bitopertin 30 mg: 40.7 (9.4) Bitopertin 60 mg: 38.9 (9.5) Placebo: 39.0 (10.8)	NR	Bitopertin 10 mg: 25.8 (9.3) Bitopertin 30 mg: 28.5 (9.4) Bitopertin 60 mg: 27.0 (9.6) Placebo: 26.2 (9.8)
Fleischhacker et al 2019[19] (Multinational)	2012–005485-36	456	NR	26 weeks	NR	NR	NR	NR
Nemeth et al 2017[20] (Multinational)	2012–005485-36	460	NR	26 weeks	Cariprazine: 54 Risperidone: 61	Cariprazine: 40.2 (10.5) Risperidone: 40.7 (11.2)	Cariprazine: 11.98 (8.14) Risperidone: 12.96 (9.17)	NR
Hasan et al 2017[21] (Germany)	NCT00783120	73	NR	3 weeks	82.2	Active rTMS: 33.88 (8.88) Sham rTMS: 36.00 (9.86)	NR	NR
Wobrock et al 2015[22] (Germany)	NCT00783120	175	NR	3 weeks	75.2	Active rTMS: 36.2 (10.5) Sham rTMS: 34.9 (9.1)	NR	NR
Hill et al 2011[23] (United States)	NR	32	Outpatient	12 weeks	Folate: 76.5 Placebo: 86.7	Folate: 45.5 Placebo: 46.5	Folate: 20.1 (10.9) Placebo: 19.1 (11.3)	NR
Hirayasu et al 2016[24] (Japan)	JapicCTI-111627	105	Outpatient	52 weeks	68	Bitopertin 5 mg: 41.8 (11.9) Bitopertin 10 mg: 39.9 (12.2) Bitopertin 20 mg: 41.8 (13.8)	NR	NR
Kane et al 2012[25] (United States)	NCT00772005	285	NR	24 weeks	Armodafinil: 75% Placebo: 64%	Armodafinil 43.8 (10.55) Placebo 42.4 (10.07)	Armodafinil: 18.0 (10.96) Placebo: 16.7 (9.86)	NR

(*Continued*)

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Table 1 (Continued).

Study	Study Number	Patients, n	Inpatient/ Outpatient	Planned Duration of Treatment	Male, %	Mean (SD) age, years	Mean (SD) Duration of Disease, Years	Mean (SD) age at Diagnosis, Years
Kaphzan et al 2014[26] (Israel)	NCT00192855	50	NR	12 weeks	73.3	Entacapone: 41.8 (2.7) Placebo: 43.8 (2.3)	Entacapone: 18.7 (10.4) Placebo: 18.9 (12.8)	NR
Kayo et al 2020[27] (Brazil)	NCT00791882	62	Outpatient	20 weeks	70.9	NR	16.3 (SD not reported)	NR
Klingberg et al 2011[28] (Germany)	ISRCTN 25455020	198	Outpatient	9 months	56.1	36.9 (9.9)	NR	NR
Klingberg et al 2012[29] (Germany)	ISRCTN 25455020	198	NR	9 months	56.1	36.9 (9.9)	NR	NR
Levkovitz et al 2011[30] (Israel)	NR	15	NR	4 weeks	73.3	32.73 (11.18)	NR	24.86 (10.69)
Liu et al 2012[31] (Taiwan)	NA	50	Inpatients	NA	46	31.1 (7.5)	8.1 (5.9)	21.6 (6.3)
Mairs et al 2011[32] (United Kingdom)	NR	8	NR	NR	75	33 (9.2)	6.1 (5.1)	NR
Novick et al 2017[33] (Multinational)	NA	3,712	Outpatient	NA	Olanzapine: 59.4 Other atypicals: 55.7 Typicals: 53.8	Olanzapine: 38.6 (12.6) Other atypicals: 40.1 (12.4) Typicals: 40.9 (11.9)	Olanzapine: 10.5 (10.5) Other atypicals: 11.7 (10.8) Typicals: 12.5 (10.3)	Mean (SD) age at first contact: Olanzapine: 28.4 (10.1) Other atypicals: 28.5 (10.1) Typicals: 28.6 (9.7)
Palm et al 2016[34] (Germany)	NCT01378078	20	NR	2 weeks	75	36.1 (11.4)	10.5 (9.9)	28.5 (10.6)
Priebe et al 2016a[35] (United Kingdom)	ISRCTN842165587	275	Outpatient	10 weeks	74	42.2 (10.7)	Median 12.6 (IQR, 9.1)	NR

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Priebe et al 2016b[36] (United Kingdom)	ISRCTN842165587	275	Outpatient	10 weeks	74	42.2 (10.7)	Median 11 (IQR 7 to 18)	NR
Savill et al 2016[37] (United Kingdom)	ICTRN842165587	275	Outpatient	Approx. 3 months	73.8	42.2 (10.65)	13.6 (9.1)	NR
Rabinowitz et al 2013[38] (United States)	NR	577	76% outpatient	Up to 18 months	NR	NR	NR	NR
Rabinowitz et al 2019[39] (Multinational)	NR	244	NR	12 weeks	NR	NR	NR	NR
Rohricht et al 2011[40] (United Kingdom)	NR	18	Outpatient	10 weeks	88.9	41.2 (11.4)	18.5 (8.4)	NR
Schaefer et al 2020[41] (Germany)	NCT00148616	13	Inpatient	24 weeks	84.6	Memantine: 26.1 (6.4) Placebo: 26.8 (6.7)	NR	Memantine: 20.7 (3.8) Placebo: 20.3 (1.4)
Schoemaker et al 2014[42] (Multinational)	NCT00725075	215	NR	12 weeks	62.1	Org 25,935 4.8 mg BID: 37.4 (9.5) Org 25,935 12–16 mg BID: 38.8 (11.0) Placebo: 38.1 (10.5)	NR	NR
Shoja Shafti et al 2016[43] (Iran)	NR	50	Inpatients	8 weeks	100	Modafinil 42.18 (5.91) Placebo 39.36 (6.37)	Modafinil: 12.30 (3.78)Placebo: 11.47 (4.23)	NR
Stauffer et al 2013[44] (Multinational)	NR	167	Both	16 weeks	77.4	43.3 (10.71)	18.3 (11.25)	NR
Sum et al 2018[45] (Singapore)	NR	58	NR	N/A	63.8	34.24 (9.25)	8.02 (8.32)	26.22 (6.91)
Valiengo et al 2020[46] (Brazil)	NCT02535676	100	NR	5 days	80	Active tDCS group: 34.6 (8.4) Sham tDCS group: 35.9 (10.1)	Active tDCS group: 14.2 (8.1)Sham tDCS group: 14.1 (8.7)	NR
Walling et al 2016[47] (Multinational)	NCT01488929	477	Outpatient	24 weeks	62.3	TC5619 5 mg: 40.0 TC5619 50 mg: 38.4 Placebo: 38.6	NR	NR

Abbreviations: NR, not reported; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; tDCS, transcranial direct current stimulation.

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Table 2 Functional Outcome Measures Identified in the Literature Review

Study	Study Number	PSP	GAF	UPSA-B	Objective Social Outcomes Index (SIX)	Sheehan Disability Scale	Social Network Schedule	Time Use Survey	GAS	Index of Functioning	Social Functioning Scale	Social Skills Inventory	SOFAS	WHO-DAS 2.0	Work and Social Adjustment Scale
Total number publications		11	7	3	2	2	2	2	1	1	1	1	1	1	1
Total number of studies		10	5	3	1	2	1	1	1	1	1	1	1	1	1
Beck et al 2013[11] (United States)	NR			✓											
Bryl et al 2020[12] (United States)	NR					✓								✓	
Buchanan et al 2012[13] (Multinational)	NCT00212836 NCT00265343 NCT00145496 NCT00174265														
Burgarski-Kirola et al 2017[14] (Multinational)	NCT01192906 NCT01192867	✓													
Dunayevich et al 2017[15] (Multinational)	NCT01568216 and NCT01568229	✓				✓									
Edgar et al 2014[16] (Multinational)	NCT00616798	✓													
Rofail et al 2016[17] (Multinational)	NCT00616798	✓													
Umbricht et al 2014[18] (Multinational)	NCT00616798	✓													
Fleischhacker et al 2019[19] (Multinational)	2012–005485-36	✓													
Nemeth et al 2017[20] (Multinational)	2012–005485-36	✓													
Hasan et al 2017[21] (Germany)	NCT00783120		✓												

Wobrock et al 2015[22] (Germany)	NCT00783120		✓												
Hill et al 2011[23] (United States)	NR		✓												
Hirayasu et al 2016[24] (Japan)	JapicCTI-111627	✓													
Kane et al 2012[25] (United States)	NCT00772005	✓													
Kaphzan et al 2014[26] (Israel)	NCT00192855														
Kayo et al 2020[27] (Brazil)	NCT00791882											✓			
Klingberg et al 2011[28] (Germany)	ISRCTN 25455020		✓												
Klingberg et al 2012[29] (Germany)	ISRCTN 25455020		✓												
Levkovitz et al 2011[30] (Israel)	NR												✓		
Liu et al 2012[31] (Taiwan)	NA														
Mairs et al 2011[32] (United Kingdom)	NR														✓
Novick et al 2017[33] (Multinational)	NA														
Palm et al 2016[34] (Germany)	NCT01378078														
Priebe et al 2016a[35] (United Kingdom)	ISRCTN84216587				✓		✓	✓							
Priebe et al 2016b[36] (United Kingdom)	ISRCTN842165587				✓		✓	✓							
Savill et al 2016[37] (United Kingdom)	ICTRN842165587														

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Table 2 (Continued).

Study	Study Number	PSP	GAF	UPSA-B	Objective Social Outcomes Index (SIX)	Sheehan Disability Scale	Social Network Schedule	Time Use Survey	GAS	Index of Functioning	Social Functioning Scale	Social Skills Inventory	SOFAS	WHO-DAS 2.0	Work and Social Adjustment Scale
Rabinowitz et al 2013[38] (United States)	NR									✓					
Rabinowitz et al 2019[39] (Multinational)	NR	✓													
Rohricht et al 2011[40] (United Kingdom)	NR										✓				
Schaefer et al 2020[41] (Germany)	NCT00148616								✓						
Schoemaker et al 2014[42] (Multinational)	NCT00725075		✓												
Shoja Shafti et al 2016[43] (Iran)	NR														
Stauffer et al 2013[44] (Multinational)	NR	✓		✓											
Sum et al 2018[45] (Singapore)	NR														
Valiengo et al 2020[46] (Brazil)	NCT02535676		✓												
Walling et al 2016[47] (Multinational)	NCT01488929			✓											

Abbreviations: GAF, Global Assessment of Functioning; GAS, Global Assessment Scale; NR, not reported; PSP, Personal and Social Performance Scale; SOFAS, Social and Occupational Functioning Assessment; UPSA-B, University of California San Diego Performance-Based Skills Assessment Brief Version; WHO-DAS 2.0, World Health Organization Disability Assessment Scale 2.0.

ranging from 0 to 100, with a higher score indicating a higher level of functioning.[48] Validation studies of the PSP have been performed across a number of different countries and patient groups, including those with stable schizophrenia, acute schizophrenia, inpatients and outpatients and both adults and adolescents. The PSP has consistently demonstrated satisfactory psychometric properties across validation studies.[50–58]

For functional outcomes, the secondly most commonly used instrument identified was the GAF, which was used in a total of seven publications[21–23,28,29,42,46] covering five individual studies. However, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) released in 2013, revisions included the removal of the GAF as an assessment of functioning, with the WHODAS 2.0 now recommended instead.[59] Despite this recommendation, the review only identified one article that cited the use of the WHODAS 2.0 (Bryl et al 2020),[12] although this may partially reflect the fact that the time frame of the review means that many of the included trials may have been designed prior to the publication of this recommendation.

Three articles identified in the review assessed functional outcome using the brief version of the University of California San Diego Performance-Based Skills Assessment (UPSA).[11,44,47] The UPSA brief version was developed by Mausbach et al[60] who describe it as a "performance-based functional outcome measure". The participant is requested to role-play a number of everyday tasks such as making an appointment or paying a bill and the brief version takes around 10−15 minutes to complete. However, the UPSA may be considered as a measure of functional capacity (the ability to perform a task) rather than a measure of functional outcome (whether the task is performed in a real-world environment).[61] Further, functional capacity may not always be an accurate reflection of functional performance.[62] However, one advantage of this type of measurement is that it is not subject to recall bias.[63]

Two articles (covering one study) reported using three different functional outcome measures, which were the Objective Social Outcomes Index, Social Network Schedule and the Time Use Survey.[35,36] The use of the Sheehan Disability Scale was also reported in two articles (covering three studies).[12,15] The use of seven further measures was reported in one article each (the Global Assessment Scale [GAS],[41] the Index of Functioning,[38] the SOFAS,[30] the Social Functioning Scale [SFS],[40] the Social Skills Inventory,[27] the WHODAS 2.0,[12] and the Work and Social adjustment Scale).[32]

Quality of Life Assessment Measures

The literature review identified a total of eleven different measures of QoL that have been used in studies in people with NSS (Table 3). The identified measures included both generic scales such as the EQ-5D as well as measures more specific to schizophrenia such as the Heinrich Carpenter Quality of Life Scale (QLS) and the Schizophrenia Quality of Life Scale (SQLS). The most frequently used measures of QoL identified in the review included the Manchester Short Assessment of Quality of Life (MANSA), the use of which was reported in four articles covering two studies.[35–37,40], the QLS (reported in three articles covering six studies),[13,23,26] with an abbreviated version of the QLS developed by Bilker et al[64] used in one further article,[11] the EQ-5D (reported in three articles covering two studies),[35,36,44] the SQLS (reported in three articles covering a single study)[16–18] and the long- and short-form versions of the Subjective Well Being Under Neuroleptic Treatment[34,44] (used in one study each). Of these, the MANSA, QLS and the SLQS are specific to people with schizophrenia. The MANSA was developed by Priebe et al as an abbreviated and modified version of the Lancashire Quality of Life Profile. It is an interviewer-administered scale that consists of sixteen questions and takes approximately 3–5 minutes to administer.[65] The QLS, developed by Heinrichs et al, is also an interviewer-administered scale and takes approximately 45 minutes to administer.[66] It consists of 21 items covering four areas (interpersonal relations, instrumental role, intrapsychic foundations and common objects and activities) and is aimed primarily at outpatients as it contains items relating to work. The SQLS was developed by Wilkinson et al and is a 30-item self-reported questionnaire that takes approximately 5–10 minutes to complete.[67] In contrast, the EQ-5D is a generic measure that assesses QoL across five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Two versions of the EQ-5D exist, the EQ-5D-3L, wherein responses are measured on a three-point scale, and the EQ-5D-5L, wherein responses are measured on a 5-point scale. The 5L version was introduced in 2009 with the aim of improving sensitivity and reducing ceiling effects.[68] EQ-5D validation studies have been performed in mental health conditions including schizophrenia. The authors of a 2004 validation study reported that the 3L version showed "acceptable construct validity" in people with schizophrenia.[69] However, validation studies have also

Table 3 Quality of Life Measures Identified in the Literature Review

Study	Study Number	MANSA	EQ-5D	QLS	SQLS	Subjective Well-Being Under Neuroleptic Treatment-Short Form	Psychological General Well-Being Schedule/ Index	Quality of Life Scale, abbreviated (Bilker et al 2003)	Q-LES-Q-18 Quality of Life Index	SF-12	SF-6D	WHOQOL BREF
Number of publications,		4	3	3	3	2	1	1	1	1	1	1
Number of studies		2	2	6	1	2	1	1	1	1	1	1
Beck et al 2013[11] (United States)	NR							✓				
Bryl et al 2020[12] (United States)	NR											
Buchanan et al 2012[13] (Multinational)	NCT00212836 NCT00265343 NCT00145496 NCT00174265			✓								
Burgarski-Kirola et al 2017[14] (Multinational)	NCT01192906 and NCT01192867											
Dunayevich et al 2017[15] (Multinational)	NCT01568216 and NCT01568229								✓			
Edgar et al 2014[16] (Multinational)	NCT00616798				✓							
Rofail et al 2016[17] (Multinational)	NCT00616798				✓							
Umbricht et al 2014[18] (Multinational)	NCT00616798				✓							
Fleischhacker et al 2019[19] (Multinational)	2012–005485-36											
Nemeth et al 2017[20] (Multinational)	2012–005485-36											

Hasan et al 2017[21] (Germany)	NCT00783120											
Wobrock et al 2015[22] (Germany)	NCT00783120											
Hill et al 2011[23] (United States)	NR			✓								
Hirayasu et al 2016[24] (Japan)	JapicCTI-111627											
Kane et al 2012[25] (United States)	NCT00772005											
Kaphzan et al 2014[26] (Israel)	NCT00192855			✓ (assumed)								
Kayo et al 2020[27] (Brazil)	NCT00791882											
Klingberg et al 2011[28] (Germany)	ISRCTN 25455020											
Klingberg et al 2012[29] (Germany)	ISRCTN 25455020											
Levkovitz et al 2011[30] (Israel)	NR											
Liu et al 2012[31] (Taiwan)	NA											
Mairs et al 2011[32] (United Kingdom)	NR											
Novick et al 2017[33] (Multinational)	NA											
Palm et al 2016[34] (Germany)	NCT01378078					✓						
Priebe et al 2016a[35] (United Kingdom)	ISRCTN84216587	✓	✓									

(*Continued*)

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Table 3 (Continued).

Study	Study Number	MANSA	EQ-5D	QLS	SQLS	Subjective Well-Being Under Neuroleptic Treatment-Short Form	Psychological General Well-Being Schedule/ Index	Quality of Life Scale, abbreviated (Bilker et al 2003)	Q-LES-Q-18 Quality of Life Index	SF-12	SF-6D	WHOQOL BREF
Priebe et al 2016b[36] (United Kingdom)	ISRCTN842165587	✓	✓									
Savill et al 2016[37] (United Kingdom)	ICTRN842165587	✓										
Rabinowitz et al 2013[38] (United States)	NR									✓	✓	
Rabinowitz et al 2019[39] (Multinational)	NR											
Rohricht et al 2011[40] (United Kingdom)	NR	✓										
Schaefer et al 2020[41] (Germany)	NCT00148616											
Schoemaker et al 2014[42] (Multinational)	NCT00725075											
Shoja Shafti et al 2016[43] (Iran)	NR						✓					
Stauffer et al 2013[44] (Multinational)	NR		✓			✓						
Sum et al 2018[45] (Singapore)	NR											✓
Valiengo et al 2020[46] (Brazil)	NCT02535676											
Walling et al 2016[47] (Multinational)	NCT01488929											

Abbreviations: MANSA, Manchester Short Assessment of Quality of Life; QLS, Quality of Life Scale; SQLS, Schizophrenia Quality of Life Scale; WHOQOL-BREF, World Health Organization Quality of Life Brief Assessment.

suggested that there may be a ceiling effect in the EQ-5D index score, suggesting that it may have limited sensitivity in those with less severe disease.[70]

The other QoL measures identified in the review were the Psychological General Well-Being Schedule,[43] World Health Organization Quality of life Scale Brief Version,[45] the Quality of Life Enjoyment and Satisfaction Questionnaire,[15] SF-12,[38] and the SF-6D.[38]

Discussion

Patient-reported outcomes including functional outcome and QoL are increasingly recognized as important endpoints.[71] In people with NSS, a greater severity of negative symptoms has been linked with worse functional outcome[8] and there has been some discussion as to whether functional outcome should be included as a co-primary endpoint in trials of interventions targeting NSS.[72] In the studies identified in the current review functional outcome was typically presented as a secondary, exploratory or ancillary endpoint rather than a primary endpoint.

Decisions relating to which instruments to use to assess functional outcomes and QoL may be influenced by several factors including, the recall period, the total time required for completion, whether the instrument is generic or disease-specific and whether it is self-reported or interviewer-administered. With regard to the choice of self-reported versus interviewer-reported measures, some advantages associated with self-reported measures include low cost and low time requirements for investigators. However, limitations include the risk of recall bias, particularly over longer recall periods[73] and reliability.[74] A strength of interviewer-administered questionnaires is higher response rates[75] but limitations include the potential for inter-rater variability and longer time requirements. For example, the full version of the UPSA may take up to 30 minutes to complete and such a lengthy time requirement may limit the practicality of such measures for large studies. Additionally, instruments used to assess QoL and functional outcome may be either generic or specific to particular conditions. The use of generic measures allows comparison with other disease areas, and some generic QoL instruments such as the EQ-5D or SF-6D allow utility scores to be determined, which can then be used to inform health economic modeling analyses. However, a limitation of generic measures is that they may not be nuanced enough to detect small but meaningful changes in signs or symptoms specific to particular conditions.[76]

An earlier review by Burns and Patrick (2007)[77] also investigated functional outcome measures used in schizophrenia studies (not limited to individuals with NSS), published over the period 1990–2006. Burns and Patrick identified a total of 87 different measures used across a total of 301 studies with the GAF, GAS and SFS being the most frequently used measures. The PSP was only used in three studies included in the earlier review; however, this likely reflects the timeframe of the review, which largely covered a period prior to the introduction of the PSP in 2001. Burns and Patrick also noted that "a striking lack of data on psychometric properties was observed". This situation is now being remedied as validation studies have become available for the majority of measures identified in the present review, although the number of published validation studies varied considerably between different measures. However, validation studies specific to groups of people with prominent NSS are still lacking.

Another review by Karow et al[78] characterized QoL measures used in schizophrenia studies published over the period 2009–2013. Karow et al identified a total of 35 different QoL measures used across a total of 432 studies. In this earlier review, the most commonly used condition-specific measures were the Heinrich Carpenter Quality of Life Scale and the Q-LES-Q-18. The most frequently used generic measures were the WHOQOL-BREF, SF-36 and SF-12. Notably, Karow et al reported that over 50% of the studies included in their review listed QoL as a primary endpoint. This contrasts with the findings of the current review wherein QoL was typically reported as a secondary or exploratory/ancillary endpoint. In another more recent review, Azaiez et al[79] identified a total of nineteen different QoL measures used across schizophrenia studies. However, they noted that none of the studies included in the review were specific to people with NSS and also highlighted a lack of validation studies for QoL measures specifically in groups of people with NSS.

The focus of the present review was to identify instruments used to measure QoL and functional outcomes in studies conducted in people with NSS. However, ecological momentary assessment (EMA) methods, also known as experience sampling assessment have been used to assess day-to-day activity and functioning in people with schizophrenia. EMA typically utilizes smartphones or wearable activity trackers to either passively or actively monitor activity. Passive monitoring involves the discreet collection of data such as GPS data whereas active monitoring involves collection of self-reported data via questions relating to current or recent activities, interactions or mood. As such, EMA can provide real-time information relating to a number

of different aspects of functioning and daily life (eg, social activities, employment or education, self-care and home care).[80] A key strength of EMA is that it largely overcomes the recall bias that self-reported measures are susceptible to, as these can require the respondent to accurately recall events over the preceding week or month.[81] In a 2020 study, Granholm et al[80] used a smartphone-based system to ask questions (at a frequency of seven times per day) relating to activities and functioning in the previous hour. The questions posed included activities such as shopping, using a bank or ATM, grooming, and interactions with family, friends or colleagues. The authors reported that EMA was a reliable and valid method for assessing functioning in people with schizophrenia.[80] However, limitations of EMA are that active EMA requires the cooperation of the respondent, potentially several times per day, for the duration of the study,[81] and also, EMA alone may not sufficient to capture subtle changes or nuances of NSS. Lopez-Morinigo et al[82] also draw attention to the role of monetary incentives in terms of influencing acceptability. Lopez-Morinigo et al also reported that in their study, which offered no monetary incentive for responses, the acceptability of EMA in people with schizophrenia spectrum disorders was low at just 31%, and that acceptability was influenced by age, educational level, early adolescent premorbid adjustment, insight and executive functioning.[82]

Overall, the findings of the review show that in studies conducted in people with NSS and published from 2011 onwards a total of fourteen different instruments used to assess functional outcomes and eleven different measures used to assess QoL were identified. The large number of measures available permits study designers to select an instrument that meets the requirements of the study. For example, whether to use a generic scale to allow greater comparability or a condition-specific scale that is more nuanced and may have greater sensitivity in terms of changes in condition-specific signs and symptoms. Similarly, if time constraints are a factor, study designers may opt for either self-reported measures or abbreviated versions of interviewer-rated scales. The current review showed that the PSP was the most frequently used functional outcome measure used in recent studies conducted in people with NSS. Further, multiple linguistic and cultural validation studies of the PSP report that it has satisfactory psychometric properties. Similarly, the most frequently used measures for assessing QoL including the MANSA, the QLS, the SQLS and the EQ-5D. The most extensively validated QoL measure specific to people with schizophrenia is the SQLS. However, across both functional outcome and QoL measures there is a general paucity of validation studies specific to groups of people with prominent NSS.

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