REVIEW ARTICLE

Effectiveness of late-life depression interventions on functional limitations: A systematic review

Sanne Wassink-Vossen,1 Richard C. Oude Voshaar,2 Paul Naarding1 and Rose M. Collard3

1Department of Old-age Psychiatry, GGNet, Apeldoorn/Zutphen, 2University Medical Center Groningen, University Center for Psychiatry, University of Groningen, Groningen, and 3Department of Psychiatry, Radboud University Medical Centre, Nijmegen, The Netherlands

ABSTRACT: Depression is one of the most prevalent mental disorders in older adults and leads to considerable decreases in health, well-being, and impaired functioning. Intervention studies have focused on the effects on symptomatic recovery, and most do not include functional recovery as an outcome. Reduction of functional limitations as a treatment goal in old-age psychiatry aligns with the values of older persons. The objective of this review was therefore to evaluate the effectiveness of late-life depression interventions on functional limitations. This systematic review identified 15 randomized controlled trials in which the effectiveness of different interventions on functional limitations was evaluated in patients with late-life depression. The interventions were categorized into four categories: psychological interventions, drug treatment, physical exercise, and collaborative care. Multicomponent and collaborative-care interventions appear to be the most promising for improvement of functional limitations, particularly in primary care and community-dwelling populations of older persons with symptoms of depression. There is, however, a lack of evidence regarding studies in specialized mental health care.

KEY WORDS: depression, mental health recovery, nursing care, psychiatry, systematic review.

INTRODUCTION

Depression is one of the most prevalent mental disorders and leads to considerable decreases in health, well-being, and daily functioning (disability). While the largest proportion of the years of life lived with disabilities (YLDs) due to depressive disorders occurs at working ages, the Global Burden of Disease studies shows that depression in later life still accounts for 6.1 million YLDs among persons aged 65 years and over (Ferrari et al. 2013). This will only increase over the next decades due to a shifting demographical balance. Pooled prevalence rates of depressive disorder vary from 1.8% to 7.2% among community-dwelling older adults (Beekman et al. 1999; Luppa et al. 2012). The prognosis of depression deteriorates with increasing age (Schaaks et al. 2018). Meta-analyses of randomized controlled trials on the effectiveness of antidepressants demonstrated significantly lower effect-sizes in older adults compared to younger adults (Tedeschini et al. 2011). This is further substantiated in a meta-regression analyses of studies in older depressed samples, which shows that increasing age is associated with lower treatment responses (Calati et al. 2013). Despite the lack of direct comparisons between younger and older adults within stratified randomized controlled trials, comparisons of the course of depression between...
The concept of functioning, functional limitations or disability, pertains to how people function in everyday life, in the performance of activities, and in the areas of life in which they participate (Bickenbach 2012). This differs from concepts such as quality of life and well-being because these are broad concepts that may be affected by disability, but that also depend on people’s assessment of several other factors (Hudelson 1994). Worldwide, more than 46% of persons aged 60 years and over have disabilities and more than 250 million older persons experience moderate to severe disability (United Nations, Department of Economic & Social Affairs, Population Division 2015). Poor functional recovery after treatment of depression may be explained by shared determinants such as chronic medical illnesses and cognitive impairment (Alexopoulos et al. 2005; Baune et al. 2007; Comijs et al. 2011), as well as by a two-way association between late-life depression and functional limitations (Lenze et al. 2001): depression negatively impacts functioning (Cronin-Stubbs et al. 2000) and functional limitations are associated with persistent depression (Lenze et al. 2001; Licht-Strunk et al. 2007).

From the patient’s perspective, functional recovery is regarded as an important treatment outcome (Zimmerman et al. 2006). In the recent years, there has been a call for a reformulation of the concept of ‘health’ as the ability to adapt and self-manage in the face of social, physical and emotional challenges (Huber et al. 2011). Both patient organizations as well as governmental institutions argue for new approaches that are tailored to improve mental health care and reinforce self-management by patients (European Commission 2020; Minl 2020; Rijksoverheid 2020). For patients, the core of recovery is not the absence of an illness, for example depression, but rather the ability to ‘rise above the diagnostic label’ (Boevink 2012). Primary outcomes of depression treatment studies mainly focus on remission and severity of depressive symptoms, even though outcome measures such as functional limitations may be of equal, if not higher importance. To date, reviews of intervention studies in late-life depression have focused on the effect on symptomatic recovery and did not include functional recovery as an outcome (Langlieb & Guico-Pabia 2010), or found limited effect on functional disability in older adults with physical comorbidities (Frost et al. 2019). Such knowledge would be relevant, because the addition of interventions with a positive effect on functional recovery could improve the prognosis of late-life depression.

An important step is to review and assess the effect of late-life depression interventions on functional limitations, while also taking the quality of the studies into account. The objective of this review was therefore to evaluate the effectiveness of late-life depression interventions on functional limitations.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2015). The research objectives, search strategy, and data-extraction sheets were a prior approved by all authors and have not been adapted during the study period.

Inclusion and exclusion criteria

This review considered intervention studies with a randomized controlled design, including older adults with depressive disorders and with functional limitations/recovery as primary or secondary outcome. Inclusion criteria for the studies were: (a) older adults with a mean age ≥65 years; (b) with any type of depressive disorders/symptoms confirmed by a (self-report) depression scale, by the International Statistical Classification of Diseases (ICD 10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria; (c) receiving interventions (any dosage or duration) for depression, (d) with outcome measured as functional limitations/disability. Studies into patient samples with another illness as the primary diagnosis (e.g. bipolar disorder, psychosis, dementia, stroke survivors, diabetes, heart failure, cancer) or other subgroups (e.g. war veterans) were excluded.

Study outcome

Because depression is related to functional decline across several domains, the outcome of interest was a change in functional status, measured by any self-reported or observer-rated functional disability scale. Studies that only used quality of life measures were not included.
Search strategy

Studies were identified through a systematic literature search including articles up until April 2021. The databases PubMed and CINAHL served as the primary source for original studies. Search terms included keywords for depression in combination with keywords for functional limitations and clinical trials: (‘Depression’[Mesh] OR ‘Depressive Disorder, Treatment-Resistant’[Mesh] OR ‘Depressive Disorder, Major’[Mesh]) AND ‘Aged’[Mesh]) AND (‘Clinical Trials as Topic’[Mesh] OR ‘Controlled Clinical Trial’ [Publication Type]) AND (functional limitations OR WHODAS OR Sheehan OR impairment OR disability). Only articles that were written in English or Dutch were included. We did not pose any restriction with respect to year of publication.

Study selection

All studies were selected and evaluated for eligibility based on the title and abstract, independently by two authors (Author 1 and Author 4). Subsequently, full-text evaluation of the studies was performed by the same two authors. In the rare case of disagreement, a third author (Author 2) was included in the discussion and consensus was reached.

Quality assessment

Studies that met the inclusion criteria were evaluated in terms of methodological quality using the Cochrane Risk of Bias assessment tool (RoB 2), which addresses specific domains that may influence the risk of bias in an RCT (Higgins et al. 2011). The five domains for individually randomized trials are: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. The tool includes algorithms that map responses to signalling questions onto a proposed risk-of-bias judgement for each domain. These domain-level judgements provide the basis for an overall risk-of-bias judgement for the specific trial result being assessed. The overall risk-of-bias levels are: (1) low risk of bias (the study is considered to be at low risk of bias in at least one domain for this result, or the study is considered to have concerns regarding multiple domains that substantially lower confidence in the result) (Higgins et al. 2019). The quality appraisal was also independently conducted by two authors (Author 1 and Author 4).

Data extraction

Participants and study characteristics including mean age, gender distribution, recruitment setting and depression measure were extracted from the selected studies. Change in functional limitations (pre-post-test and between groups) was assessed using the functional-limitations scales that were applied. Information related to the therapy including setting, content, duration and frequency of sessions, control condition and mode of delivery were also extracted from the included studies.

In the case of more than one intervention group (e.g. in-person problem solving therapy (PST) and PST via telephone or two types of exercise versus medication), all treatment groups were reviewed separately with regard to the effect on functional limitations. Studies were grouped by type of intervention.

RESULTS

Search results

The search strategy yielded 510 articles in PubMed and 478 in CINAHL. After removing duplicates, 583 records remained. The initial title and abstract screening led to the exclusion of 170 out of 220 articles that did not meet the inclusion-criteria. We examined 50 full-text articles, of which ten articles were included (exclusion reasons: no formal measure of depression \( n = 2 \); subgroup \( n = 1 \); no formal measure of functional limitations \( n = 9 \); only baseline measures of functional limitations available \( n = 4 \); only physical functioning was measured \( n = 2 \); adult population \( n = 8 \); no subgroup analysis of older population \( n = 9 \); design was not an RCT \( n = 2 \); meta-analysis \( n = 2 \); double study \( n = 1 \)).

In the selected articles, the Short Form Health Survey questionnaire (SF-36/12 or RAND) from the Medical Outcome Study was frequently used to measure disability (Tarlov et al. 1989). After this observation, a post-hoc search was conducted including terms of (SF or RAND) and (rehabilitation). The (SF or RAND) search resulted in five additional studies.
This led to the selection of fifteen RCTs on interventions in late-life depression with effectiveness on functional limitations as the outcome measure (see Fig. 1: flowchart).

Study characteristics

Fifteen studies included a total of $n = 4285$ participants, which varied for each study from $n = 25$ (Alexopoulos et al. 2003) to $n = 1801$ (Unutzer et al. 2002). Six studies included community-dwelling older adults (Brenes et al. 2007; Choi et al. 2014, 2020; Gitlin et al. 2013; Huang, et al. 2015b; Kiosses et al. 2010), five studies were conducted in primary care (Gilbody et al. 2017; van Marwijk et al. 2008; Unutzer et al. 2002; Williams et al. 2000) of which one in combination with a mental health care institute (Neviani et al. 2017) and two studies were conducted in a nursing home/senior centre (Gitlin et al. 2013; Rondanelli et al. 2011). The majority of the studies took place in the USA. Five out of fifteen in other countries: Italy (Neviani et al. 2017; Rondanelli et al. 2011), The Netherlands (van Marwijk et al. 2008), the United Kingdom (Gilbody et al. 2017) and Taiwan (Huang et al. 2015b). Table 1 summarizes the description included studies.

Population

The mean age of the populations varied from 65 (Choi et al. 2014) to 78 years (Rondanelli et al. 2011) with varying sex distribution from 41% women (Williams et al. 2000) to 100% (Rondanelli et al. 2011). Six studies included participants with major depression (Alexopoulos et al. 2003, 2011, 2015; Kiosses et al. 2010; van Marwijk et al. 2008; Neviani et al. 2017), two studies focused on a combination of major depression and/or dysthymia (Rondanelli et al. 2011; Unutzer et al. 2002), one study included participants with minor depression or dysthymia (Williams et al. 2000), one study included
| First author, year of publication | Total N | Type of study | Population main inclusion criteria: depression (measurement) | Characteristics | Gender | Setting (Recruitment)/ country | Outcome on functioning | Assessment time |
|----------------------------------|---------|---------------|---------------------------------------------------------------|-----------------|--------|--------------------------------|-----------------------|-----------------|
| Alexopoulos et al. (2003)        | 25      | RCT           | major depression (HDRS)                                       |                 | 74%    | University intervention research centre (unknown) USA | WHODAS               | Baseline, 12 weeks |
| Alexopoulos et al. (2011)        | 221     | RCT           | major depression (SCID, HDRS) executive dysfunction           |                 | unknown| University intervention research centre (unknown) USA | WHODAS               | Baseline, weekly until week 12, 24, 36 weeks |
| Alexopoulos et al. (2015)        | 39      | RCT           | major depression (SCID)                                       |                 | IG: 73 | University intervention research centre (unknown) USA | WHODAS               | Baseline, 6, 9 weeks |
| Brenes et al. (2007)             | 37      | RCT           | 2–4 symptoms of depression (PHQ-9)                           |                 | IG1: 76 | Community (newspaper/ads/letters) USA | a. SF-36 physical, b. SF-36 mental, c. Q FAST | Baseline, 4 months |
| Choi et al. (2014)               | 158     | RCT           | depression (HDRS = ≥15)                                       |                 | 65 (9.2) | Community (aging service agencies) USA | WHODAS               | Baseline, 12, 36 weeks,  |
| Choi et al. (2020)               | 277     | RCT           | severe depressive symptoms (HDRS = ≥15)                      |                 | 67.5 (8.9) | Community (aging service agencies) USA | WHOAS               | Baseline, 12, 24, 36 weeks |
| Gilbody et al. (2017)            | 705     | RCT           | subthreshold depression (MINI)                                |                 | 77 (7.1) | Community (senior center, ads/brochure) USA | Q FAST               | Baseline 4, 8 months |
| Gilin et al. (2013)              | 208     | RCT           | depressive symptoms (PHQ-9 = ≥5)                              |                 | 77 (7.1) | Community (senior center, ads/brochure) USA | Q FAST               | Baseline 4, 8 months |
| Huang et al. (2015)              | 57      | RCT           | depressive mood (GDS-15 = ≥5)                                 |                 | 77 (5.9) | Community (mail/poster) Taiwan | SF-36               | Baseline, 3, 6, 9 months |
| Kiosses et al. (2010)            | 30      | RCT           | major depression (SCID and HDRS = ≥17)                        |                 | IG: 80 | Research centre (advertisement/home delivered meals program) USA | SDS                 | Baseline, 6, 12 weeks |

(Continued)
### TABLE 1

| First author, year of publication | Total N | Type of study | Population main inclusion criteria: depression(measurement) | Characteristics | Gender | Setting (Recruitment)/ country | Outcome on functioning | Assessment time |
|-----------------------------------|---------|---------------|-------------------------------------------------------------|-----------------|--------|-------------------------------|-----------------------|-----------------|
| Marwijk et al. (2008)            | 145     | RCT           | major depression (GDS-15 = 'positive' and diagnose by PRIME-MD) | Mean age: 65.6 (8.7) years (SD), % women: 83 | | Primary care (screening GP) | SF | Baseline, 2,6,12 months |
| Neviani et al. (2017)           | 121     | RCT           | Major Depression (HDRS = >18) | Mean age: 75 years, % women: 71 | | Mental Health and Primary Care, (GP and psychiatrist) Italy | BDQ | Baseline, 24 weeks |
| Bondanelli, et al. (2011)        | 46      | RCT           | Major Depression or Dysthymia (DSM-IV clinical diagnosis by senior psychiatrist) | IG: 85 (6.9) years, % women: 100; CG: 83 (7.3) years | | Nursing home (psychiatrist) Italy | SF-36 | Baseline, 8 weeks |
| Unutzer et al. (2002)            | 1801    | RCT           | major depression or dysthymia (SCID) | Mean age: 71 (7.5) years, % women: 65 | | Primary care (GP) USA | SDS | Baseline, 3, 6, 12 month |
| Williams et al. (2000)          | 415     | RCT           | minor depression or dysthymia (PRIME-MD and HDRS = ≥10) | Mean age: 71 (range 60-95) years, % women: 41 | | Primary care (research psychiatrist/psychologist) USA | SF-36 Physical | Baseline, 11 weeks |

Abbreviations: BDQ: Brief Disability Questionnaire; CG: control group; GDS-15: Geriatric Depression Scale; HAMD: Hamilton Depression Rating Scale; MCI: Mild Cognitive Impairment; PRIME-MD: PRIMary care Evaluation of Mental Disorders. Outcome (disability scales) - SDS: Sheehan Disability Scale; Q FAST: physical disability questionnaire adopted from The Fitness Arthritis and Seniors Trial (FAST). Characteristics - IG: intervention group; SF-36/SF-12: Healthy survey short form; Type of study - RCT: Randomized Controlled Trial. Population inclusion criteria – SCID: Structured Clinical Interview for DSM-IV; WHODAS: World Health Organization Disability Assessment Schedule.
participants with subthreshold depression (Gilbody et al. 2017), three studies included elderly with depressive symptoms and excluded persons with major depression (Brenes et al. 2007; Huang et al. 2015b) or severe mental illness in the past (Gitlin et al. 2013). Depression was mainly determined by screening questionnaires (Patient Health Questionnaire (PHQ-9) (Brenes et al. 2007; Gitlin et al. 2013); Geriatric Depression Scale (GDS-15) (Huang et al. 2015b; van Marwijk et al. 2008)), rating scales (Hamilton Depression Rating Scale (HDRS) (Alexopoulos et al. 2008)), or diagnostic interviews by research assistants (Structured Clinical Interview for DSM Disorders (SCID) (Alexopoulos et al. 2011, 2015; Kiosses et al. 2010; Neviani et al. 2017; Neviani et al. 2017; Williams et al. 2000)), or diagnostic interviews by research assistants (Structured Clinical Interview for DSM Disorders (SCID) (Alexopoulos et al. 2011, 2015; Kiosses et al. 2010; Unutzer et al. 2002); Mini-International Neuropsychiatric Interview (MINI) (Gilbody et al. 2017); Primary Care Evaluation of Mental Disorders (PRIME-MD) (van Marwijk et al. 2008; Williams et al. 2000)). One study included participants with a clinical diagnosis of depression diagnosed by a senior psychiatrist (Rondanelli et al. 2011).

Outcome measurements

The functional limitations outcome was defined as functional impairment (Unutzer et al. 2002), functional status (Williams et al. 2000), functional difficulty (Gitlin et al. 2013), disability (Alexopoulos et al. 2003, 2011, 2015; Choi et al. 2014, 2020; Neviani et al. 2017), physical and emotional functioning (Brenes et al. 2007) or health related functions in measuring quality of life (Gilbody et al. 2017; Huang et al. 2015b; Rondanelli et al. 2011). The outcome measurements that were used for functional improvement varied. Six studies used any form of the SF questionnaire (Brenes et al. 2007; Gilbody et al. 2017; Huang et al. 2015b; van Marwijk et al. 2008; Rondanelli et al. 2011; Williams et al. 2000), five studies used the World Health Organization Disability Assessment Schedule (WHODAS) (Alexopoulos et al. 2003, 2011, 2015; Choi et al. 2014, 2020), two studies used the Sheehan Disability Scale (SDS) (Kiosses et al. 2010; Unutzer et al. 2002), two studies used the Questionnaire from The Fitness Arthritis and Seniors Trial (Q FAST) (Brenes et al. 2007; Gitlin et al. 2013) and Neviani et al. (2017) used the Brief Disability Questionnaire (BDQ). See Table 1 for a summary of the characteristics of the included studies. For a more elaborate description of the instruments that were used with references, see Box 1: Description of instruments used to measure disability.

Risk of bias

Overall, most studies had an unclear or high risk of bias (n = 13), largely due to limited reporting of the randomization process (n = 10), missing outcome data (n = 10), and doubts regarding the selection of reported results (n = 8). Studies were most commonly at a low risk of bias for outcome assessment (n = 14). However, it should be noted that due to the nature of the psychological interventions, blinding of the participants and research staff was not possible in most of the studies. In the end, only two studies were classified with a low risk of bias. The final judgement of the risk-of-bias tool across all included studies is summarized in Table 2. The complete summary of the risk-of-bias assessment of the studies is included in Fig. 2a,b: Risk-of-bias summary. Individual risk-of-bias ratings are discussed throughout the synthesis for each outcome.

Synthesis of the effect of interventions on functioning

The interventions were grouped into psychological interventions (Alexopoulos et al. 2003, 2011, 2015; Choi et al. 2014, 2020; Huang et al. 2015b; Kiosses et al. 2010; Williams et al. 2000), drug treatment (Brenes et al. 2007; Rondanelli et al. 2011; Williams et al. 2000), exercise (Brenes et al. 2007; Huang et al. 2015b) in combination with medication (Neviani et al. 2017) and any type of collaborative care (Gilbody et al. 2017; Gitlin et al. 2013; van Marwijk et al. 2008; Unutzer et al. 2002).

The interventions evaluated were compared to a variation of control conditions, including active controls: problem solving therapy (Alexopoulos et al. 2015), supportive therapy/care calls (Alexopoulos et al. 2003, 2011; Choi et al. 2014, 2020; Kiosses et al. 2010), and sertraline (Neviani et al. 2017), as well as inactive control conditions: care as usual (Brenes et al. 2007; Gilbody et al. 2017; Huang et al. 2015b; van Marwijk et al. 2008; Unutzer et al. 2002), waiting list (Gitlin et al. 2013), and placebo (Rondanelli et al. 2011; Williams et al. 2000). Eight out of fifteen studies measured follow-up results, defined as ≥12 weeks after conclusion of the intervention. Only one study showed long-term effectiveness compared to the control group up to eight months post-intervention (Gilbody et al. 2017) (see Table 2).
Psychological interventions

Eight studies examined interventions based on cognitive-behavioural therapy (CBT) principles, embedded in problem solving therapy, including three main steps: (1) patient symptoms are linked to their everyday problems, (2) the problems are clarified and (3) patients learn skills to improve their ability to deal with specific everyday problems. Results on PST were mixed. Huang et al. (2015b) studied PST provided by a psychiatric nurse and found that PST was not effective in the short or long term, whereas Alexopoulos et al. (2003) found that the PST group had lower disability scores as compared to the control group, after twelve weeks. The six remaining studies showed a positive effect of PST on short-term disability (12 weeks) compared with supportive therapy (Alexopoulos et al. 2011; Choi et al. 2014, 2020; Huang et al. 2015b; Kiosses et al. 2010), and equal effectiveness when compared with engagement (Alexopoulos et al. 2015). Williams et al. (2000) found an effect of PST on only mental functioning in a small subpopulation. Kiossen et al. (2010) found that augmentation of PST with environmental adaptation tools and caregiver participation was more effective in lowering disability than supportive therapy. Two studies (Choi et al. 2014, 2020) compared two interventions (video conferenced PST and in-person PST and video conferenced PST and behavioural activation) with care calls, and found that PST and behavioural activation were more effective than care calls. There were no differences in the effects on disability between in-person PST and care calls. None of the studies had a low risk of bias (Table 2). The overall effect of the interventions was not persistent, since no long-term effectiveness was found in most of the studies that measured follow-up results (Alexopoulos et al. 2011; Choi et al. 2014; Huang et al. 2015b), only Choi et al. (2020) found a persisting effect at 36 weeks.

Drug treatment

Three studies measured the effect of medication on functioning in late-life depression. Two studies compared medication with a placebo (Rondanelli et al. 2005).
### TABLE 2 Summary of results grouped by type of intervention

| First author, year of publication | Intervention duration | Outcome functioning | Assessment time | Analysis† | Results | Effect | Quality ROB‡ |
|----------------------------------|-----------------------|--------------------|----------------|-----------|---------|--------|-------------|
| **Psychological interventions**  |                       |                    |                |           |         |        |             |
| Alexopoulos et al. (2003)        | 12 weekly sessions    | Psychological interventions | WHODAS Baseline, 12 week | Mixed effect models | Significant time-by-treatment interaction ($F_{1,22} = 4.44$); that is, PST led to a more rapid improvement in WHODAS-II scores. The effect size for the time-by-treatment interaction was 0.58; $P = <0.05$. The PST group had less disability (higher WHODAS-II scores) at the end of treatment than the ST group ($t_{23} = 4.69$); $P = <0.001$. | + | ● |
|                                  | Problem solving therapy ($n = 12$) | Supportive therapy ($n = 13$) | | | | |
| Alexopoulos et al. (2011)        | 12 weekly sessions    | Psychological interventions | WHODAS Baseline, weekly until week 12, 24, 36 weeks | Mixed effect models | After 12 weeks: PST participants had a significantly higher reduction in disability (total WHODAS scores) over 12 weeks than ST participants (Est. = −0.1824; $T = −2.51$; df = 202; $P = 0.01$). After 36 weeks: no significant difference between groups in the course of disability after treatment (group by time interaction: $t = 0.16$, df = 1, 142; $P = 0.66$). | – | ● |
|                                  | Problem-solving therapy ($n = 110$) | Supportive Therapy ($n = 111$) | | | | |
| Alexopoulos et al. (2015)        | 9 weekly sessions     | Psychological interventions | WHODAS Baseline, 6, 9 weeks | Mixed effect linear regression models | Both treatments reduced WHODAS; the effect of week was $F_{(2,234)} = 35.73$; $P < 0.001$. The week x treatment interaction was not significant: $F_{(2,234)} = 0.08$; $P = 0.93$. The difference between groups (after controlling for other variables) at week 9 was $0.16$ WHODAS points; $t_{234} = 0.11$ with a Cohen’s $d = 0.02$; 95% CI: $−0.35$ to $0.39$; $P = 0.91$. | + | ● |
|                                  | Engagement in meaningful, rewarding activities ($n = 39$) | Problem-solving therapy ($n = 97$) | | | | |
| Choi et al. (2014)               | 6 sessions            | Psychological interventions | WHODAS Baseline, 12, 36 weeks | Mixed effect regression models | 1) 0-12 weeks: group by time interaction effect: $B$ (SE): $−0.31$ (0.14); 95% CI: $−0.60$, $−0.03$; $t = −2.16$; $P = 0.03$ 2) 0−12 weeks: group by time interaction effect: $B$ (SE): $−0.09$ (0.14); 95% CI: $−0.36$, 0.19; $t = −0.60$; $P = 0.55$ 1/2) 12−36 weeks: Group by time interaction effects were nonsignificant for both groups. | – | ● |
|                                  | 1) video conferenced problem-solving therapy ($n = 58$) | Care calls ($n = 12$) | | | | |
|                                  | 2) Face-to-face problem-solving therapy at home ($n = 63$) | Care calls ($n = 12$) | | | | |
| Choi et al. (2020)               | 5 weekly sessions     | Psychological interventions | WHODAS Baseline, 12, 24, 36 weeks | Mixed effect regression | 1) Compared with participants in the AC group, participants in the tele-BA group had significantly reduced WHODAS scores across all follow-up assessments estimates, $−3.91$ (95% CI $−5.93$ to $−1.89$); $P < 0.001$ 2) Compared with participants in the AC group, participants in the tele-PST group | + | ● |
|                                  | 1) video conferenced BA by lay counselors ($n = 90$) | AC: Telephone support calls by research assistants ($n = 94$) | | | | |
|                                  | 2) Face-to-face problem-solving therapy at home ($n = 63$) | Care calls ($n = 12$) | | | | |

(Continued)
| First author, year of publication | Intervention duration | Outcome functioning | Assessment time | Analysis | Results | Effect | Quality ROB² |
|---------------------------------|----------------------|---------------------|----------------|----------|---------|--------|-------------|
| Huang et al. (2015)             | 12 weeks             | SF-36               | Baseline, 3, 6, 9 months | GEE      | had significantly reduced WHODAS scores across all follow-up assessments, −5.80 (95% CI −5.81 to −1.80); $P < 0.001$ |
| Kiosses et al. (2010)           | 12 weeks             | SDS                 | Baseline, 6, 12 weeks | Mixed effect models | 3 Months: treatment by time interaction ($F = 7.32$, df = 1, $P = 0.01$). |
| Williams et al. (2000)          | 11 weeks: 6 treatment sessions | a) SF 36           | Baseline, 11 weeks | Mixed models of covariance | a) no effect (NR) |
|                                 |                      | b) SF-36 M          |                |                      | b) § minor depression in the lowest tertile of baseline functioning: $4.7 (1.96)$ points; $P = 0.02$ |
| Medication                      |                      |                     |                |                      | b) § minor depression intermediate: $2.9 (1.80)$ $P = >0.05$ and high baseline function: $1.4 (1.84)$ $P = >0.05$ |
| Brenes et al. (2007)            | 16 weeks             | a) SF 36            | Baseline, 4 months | ANCOVA   | a) No effect (NR) |
|                                 |                      | a) SF 36 Ph         |                |                      | b) No effect (NR) |
|                                 |                      | a) SF-36 M          |                |                      | c) Trend towards a negative effect (ES = 0.35; $P = 0.27$). |
| Rondanelli et al. (2011)        | 8 weeks              | a) SF 36            | Baseline, 8 weeks | ANCOVA   | a) Two months: mean intervention group = 49.7; difference (95% CI): 1.59 (9.9 to 21.9) $P = <0.001$ |
|                                 |                      | b) SF-36 M          |                |                      | b) Two months: mean intervention group = 66.6; difference (95% CI): 18.3 (12.9 to 23.7) $P = <0.001$ |
| Williams et al. (2000)          | 11 weeks             | a) SF 36            | Baseline, 11 weeks | Mixed models of covariance | a) No effect |
|                                 |                      | a) SF 36 Ph         |                |                      | b) § dysthymia, in highest tertile of baseline functioning: $5.8 (2.02)$ $P = 0.01$; |
|                                 |                      | b) SF-36 M          |                |                      | b) § dysthymia, and intermediate baseline functioning: $4.4 (1.74)$ $P = 0.03$; |

(Continued)
| First author, year of publication | Intervention duration | Outcome functioning | Assessment time | Analysis | Results | Effect | Quality |
|----------------------------------|----------------------|---------------------|----------------|----------|---------|--------|---------|
| Physical exercise                |                      |                     |                |          |         |        |         |
| Brenes et al. (2007)             | 16 weeks             | Exercise (n = 14)   | Baseline, 4 months | ANCOVA   | a) No effect (NR) | –      | ●       |
|                                  |                      | Usual care calls (n = 12) |                  |          |         |        |         |
|                                  |                      | a) SF 36 Ph         | b) SF-36 36 M   | c) Q FAST |         |        |         |
| Huang et al. (2015)              | 12 weeks             | Exercise (n = 19)   | Baseline, 9 months | GEE      | c) Trend towards a positive effect (ES = −0.22; P = 0.19), +  |
|                                  |                      | Usual care (n = 20) |                  |          |         |        |         |
| Neviani et al. (2017)            | 24 weeks             | BDQ                 | Baseline, 24 weeks | GLM      | 1) Four months: changes were not significantly greater (P = 0.32), – |
|                                  |                      | 1) Sertraline + thrice weekly non-progressive exercise (n = 37) |                  |          |         |        |         |
|                                  |                      | 2) Sertraline + plus thrice-weekly progressive aerobic exercise. (n = 42) |                  |          |         |        |         |
| Collaborative care (see Box 2 for further description of the interventions) |                      |                     |                |          |         |        |         |
| Gilbody et al. (2017)            | 8 weekly sessions    | a) SF 36 Ph         | Baseline, 4 months | Linear mixed effect models | a) Four months: better physical functioning (mean score difference, −2.53 [95% CI, −4.03 to −1.62]; d = 0.2; P < 0.001) | +      | ●       |
|                                  |                      | Collaborative care (n = 344) |                  |          |         |        |         |
|                                  |                      | Usual care (n = 361) | b) SF-36 36 M   |          |         |        |         |

b) Dysthymia in low baseline functioning: 2.7 (2.17) P = >0.05; b) Minor depression in the lowest tertile of baseline functioning 4.7 (2.03) P = 0.02; b) Minor depression intermediate: 2.3 (1.65) and high baseline function: 0.2 (1.96) P = >0.05;
| First author, year of publication | Intervention duration | Outcome functioning | Assessment time | Analysis | Results | Effect +/- | Quality ROB |
|---------------------------------|----------------------|---------------------|-----------------|----------|---------|------------|------------|
| Van Marwijk et al. (2008)       | 6 months             | a) SF-36 Ph         | Baseline, 2, 6, 12 months | Analysis of variance | a) Two, six, twelve: no effect (NR) | –          | ●          |
|                                 |                      | b) SF-36 M          |                 |          |         |            |            |
|                                 |                      | Multi component disease management (n = 70) |                  |          |         |            |            |
| Unutzer et al. (2002)           | 12 months            | SDS                 | Baseline, 3, 6, 12 month | Mixed effect models | Intervention group had less health related functional impairment than control group at the three timepoints (adjusted analysis for intervention vs usual care: between-group difference or OR (95% CI); t; P value). | +          | ●          |
|                                 |                      | Usual care (n = 75) |                  |          |         |            |            |
|                                 |                      | (n = 70)            |                  |          |         |            |            |
| Collaborative care management (n = 906) | (n = 895) |                  |                  |          |         |            |            |
| Gitlin et al. (2013)            | 10 sessions          | Q-FAST              | Mixed effect models | | Improvement in intervention group compared with control for functional difficulties at four months: mean difference (95% CI) | +          | ●          |
|                                 |                      | Wait-list (n = 102) |                  |          |         |            |            |
|                                 |                      | Multi component home based intervention (n = 106) |                  |          |         |            |            |

Abbreviations: BA: behavioural activation; Interventions – AC: attention control; PATH: problem adaptation therapy; Ph: Physical domain; PST: problem solving therapy; Q FAST: physical disability questionnaire adopted from The Fitness Arthritis and Seniors Trial (FAST); SDS: Sheehan Disability Scale; SF-36/SF-12: Healthy survey Short Form (M = Mental domain; ST: supportive therapy; Outcome measurement – BDQ: Brief Disability Questionnaire; WHODAS: World Health Organization Disability Assessment Schedule.

†Analyses: ANCOVA = Analysis of covariance; GEE = Generalized estimated equations; GLM = Generalized linear models.

‡Quality ROB: The overall risk-of-bias judgements are: + (=Low risk of bias! (=Some concerns); or − (= High risk of bias).

§Because baseline mental functioning component scores interacted significantly with treatment assignment and diagnosis, these results are presented separate in mean (SE); P.
2011; Williams et al. 2000) and one with care as usual, where antidepressant use was an exclusion criterion in the control group (Brenes et al. 2007). Both Brenes et al. (2007) and Williams et al. (2000) examined selective serotonin reuptake inhibitors (SSRIs), specifically sertraline and paroxetine. The sertraline condition group (Brenes et al. 2007) experienced slight declines in physical functioning. This negative effect was not statistically significant. Paroxetine (Williams et al. 2000) was beneficial for mental health functioning only (and not physical functioning), in the middle and highest functioning groups of patients with dysthymia and in the lowest functioning group of patients with minor depression. Both studies were qualified as presenting a...
Rondanelli et al. (2011) found that omega-3 supplements had a positive effect on mental and physical functioning after two months. Risk of bias was with some concerns.

Three studies examined the effects of physical exercise on functional limitations. Two studies compared physical exercise with usual care (Breñes et al. 2007; Huang et al. 2015b), and Neviani et al. (2017) compared two types of exercise combined with an SSRI (sertraline), in comparison with medication alone. Simple exercise routines with 150 min/week (cardiovascular and muscle strength exercises) had an effect on mental and physical functioning after three months, but no long-term effect was found (Huang et al. 2015b). A similar intervention of aerobic and resistance training three times a week showed a short-term effect on mental functioning, but no effect on the physical domain of the SF (Breñes et al. 2007). This intervention did, however, have an effect on functional limitations measured with the FAST questionnaire (see Table 2). Likewise, Neviani et al. (2017) showed a short-term effect on functional limitations of progressive exercise three times a week. Non-progressive exercise did not have an effect on functional limitations. The risk-of-bias of these studies was with some concerns (Huang et al. 2015b; Neviani et al. 2017), or high risk of bias (Breñes et al. 2007).

Collaborative care

Studies were included in the collaborative-care category when the intervention was either a multicomponent mono-disciplinary intervention (Gilbody et al. 2017; Gitlin et al. 2013; van Marwijk et al. 2008) or a multidisciplinary treatment (Unutzer et al. 2002) (see Table 2 for the components of the interventions). Four studies examined collaborative care, varying from eight weekly sessions (Gilbody et al. 2017) to a twelve-month programme (Unutzer et al. 2002) and compared this intervention with usual care (Gilbody et al. 2017; van Marwijk et al. 2008; Unutzer et al. 2002) or a waiting-list control condition (Gitlin et al. 2013). All four studies were conducted in primary care. The effect on functional recovery was positive in three out of four studies (Gilbody et al. 2017; Gitlin et al. 2013; Unutzer et al. 2002) (see Table 2). All three of the studies with a positive effect on functioning included case management (by a mental health nurse, psychologist or social worker) and a multidisciplinary approach as components of the collaborative-care programme. Two of these studies had a low risk of bias.

| First author, year of publication | Intervention | Components |
|----------------------------------|--------------|------------|
| Gilbody et al. (2017) | Collaborative care: One face-to-face and four to six telephone calls by a case manager (mental health nurse or psychologist) corresponding with GP or psychiatrist | (1) support; (2) symptom monitoring; (3) structured behavioural activation program; (4) medication (continuation) |
| Gitlin et al. (2013) | Multi component home based intervention: Up to ten 1-hour in-home sessions. First weekly then biweekly for up to four months by social workers | (1) care management (systematic unmet care needs assessment; (2) referral and linkage involving resource identification; (3) linking participants to social and medical services; (4) education instructing in symptom recognition, stress reduction techniques; (5) behavioural activation (goals and plan of action) |
| Van Marwijk et al. (2008) | Multi component disease management: Once every two weeks during first two months, then monthly for four months by general practitioner | (1) standard screening/diagnosing depression; (2) education and information; (3) drug therapy; (4) supportive counselling |
| Unutzer et al. (2002) | Collaborative care management: Face-to-face or telephone calls. In acute treatment phase biweekly, in relapse prevention phase monthly by care managers/ depression clinical specialist (DCS) (nurses/ psychologists). And treatment by general practitioner or specialist in stepped care model | (1) multidisciplinary collaboration on a common definition of the problem; (2) development of therapeutic alliance; (3) personalized treatment plan; (4) proactive follow-up and outcome monitoring by depression care manager; (5) targeted use of specialty consultation; (6) protocols for stepped care/treatment (medication/psychotherapy) |
of bias (Gitlin et al. 2013; Unutzer et al. 2002), while the third study had some concerns (Gilbody et al. 2017). The mono-disciplinary disease management programme by van Marwijk et al. (2008) did not find an effect on functional status and also had some concerns regarding risk of bias.

**DISCUSSION**

**Principal findings**

This systematic review identified fifteen RCTs in which the effectiveness of interventions on reducing functional limitations was evaluated in patients with late-life depression. These RCTs evaluated a total of 20 interventions that could be categorized into four categories: psychological interventions, drug treatment, physical exercise and collaborative care. We found that the studies in the collaborative-care interventions groups showed the most similar results with regard to the effect on functional limitations in late-life depression. Studies on psychological interventions, drug treatment and physical activity showed mixed results and no definite conclusions could be drawn with regard to their impact on functional recovery in late-life depression.

**Efficacy of the interventions**

Patients with late-life depression often suffer from comorbid physical diseases (Schaakxs et al. 2018) and geriatric syndromes such as frailty (Collard et al. 2014), loneliness (Peerenboom et al. 2015) and bereavement (Shah & Meeks 2012). Despite the complicating nature of these comorbid diseases and syndromes, they are rarely, if ever, taken into account in antidepressant drug treatment trials for late-life major depression (Benraad et al. 2016). It is likely that a disease-oriented approach does not suit the complexity of these inter-related problems well. This may explain why mono-disciplinary interventions, regardless of whether they were psychotherapy, drug treatment or physical activity, were not consistently associated with functional improvement. In a collaborative-care approach, the focus is on functioning and quality of life instead of solely on managing symptoms, and this review showed that this approach improves functioning in addition to generating symptomatic improvement.

Collaborative care requires that four key criteria are met: (1) a multi-professional approach to patient care, (2) a structured management plan, (3) scheduled patient follow-ups, and lastly, (4) enhanced inter-professional communication (Gunn et al. 2006), whereas disease specific treatment can still be highly variable. The collaborative-care studies included in this review were indeed heterogeneous with respect to depression-specific treatment, but consisted of multi-component and/or multidisciplinary interventions. Since the addition of a case manager was part of the intervention in all studies with a positive effect on functioning, this implies that coordination and supervision of care is an important element in improving functional abilities in late-life depression.

The only study in which a collaborative-care intervention did not improve functional limitations was based on care provided by the general practitioner according to the current guidelines at that time (van Marwijk et al. 2008). This stepped-care approach focuses on reducing symptoms (including drug-therapy, supportive counselling, education and information) and can be regarded as disease-oriented care. While no effect on functional status was observed, they did find an effect on reduction of symptoms of depression.

Two explanations can be put forward for the lack of impact on functional status. First, it could be argued that the guideline cannot be regarded as a structured management plan, especially because implementation of depression guidelines in clinical practice is generally questionable (Bruijns et al. 2018; Sinnema et al. 2013, 2015). Second, because the general practitioner was a key person in this study, not only for providing care according to current guidelines, but also for to identifying the need of involvement of others and coordination of care, one may question whether this role for coordination of care and inter-professional communication was actually taken on. Therefore, it is likely that the key criteria of collaborative care were not met in this study.

Kiousis et al. (2010) studied PST and found that it effectively reduced functional limitations. When looking into the content of their intervention, it was noted that the environment of patients was also actively included in the treatment. We therefore make a case for categorizing this study as collaborative care instead of psychological treatment, because the intervention targeted multiple domains and met the key criteria of collaborative care.

The overarching conclusion points towards the integration of interventions such as psychological treatment into a collaborative-care framework to increase effectiveness. This could also be applied to other interventions in the physical exercise and medication categories. The mixed results with regard to the effect on functional status imply that these interventions may
be beneficial for a subgroup of depressed older persons. However, when personalized into a collaborative-care approach and augmented with specific interventions targeting the prevalent old-age phenomena, these interventions can be an important part of old-age psychiatric care with prolonged treatment results leading towards functional improvement.

This is in line with a recent review and meta-analysis by Frost et al. (2019) in which they studied the effect of non-pharmacological interventions on depressive symptoms and functioning in older persons with physical comorbidities. They found that PST had an effect on depressive symptoms, but not on functioning. With regard to collaborative care, they found that it did not reduce depressive symptoms, but that scores on the subscale of mental functioning improved. The participants in the studies who were included in the meta-analysis by Frost et al. (2019) probably had higher levels of frailty and had more somatic diseases, when compared to the studies that were included in the this review.

Methodological considerations

Population
The majority of the studies included in the present review recruited patients from community-dwelling samples or primary care (n = 13). Only two studies were conducted in a nursing home or senior centre. In the past ten years, the attention on functional status has increased, in particular due to patient involvement in treatment and shared decision-making in primary care (Archer et al. 2012; Kirkham et al. 2016). Nevertheless, the inclusion of functional status as an outcome measure is still uncommon (Beyer & Johnson 2018; Cuijpers et al. 2020; Huang et al. 2015a) in clinical trials in the area of mental health care.

The definition of depression varied from depressive symptoms to full-blown depressive disorder. The majority of the studies included participants with depressive symptoms and did not conduct a formal diagnostic procedure. This could imply that the most depressed and frail elderly were not included in the studies. Research by Markle-Reid et al. (2013) showed that the frail group benefits most from nurse-led collaborative care. The current findings are therefore likely to underrepresent the actual effect of the interventions on functional status in late-life depression.

Measuring functional disability/recovery

Very few functional assessment instruments have been validated in patients with late-life depression, and the available data are mixed. The variation in measurement of daily functioning outcomes in the old-age population was recently acknowledged in a meta-analysis by Bingham et al. (2018). Of the 21 functional assessment instruments identified by this meta-analysis, only two have been formally validated in a depressed elderly population, that is the 36-Item Short Form Survey (SF-36) (Tarlov et al. 1989) and the Performance Assessment of Self-Care Skills (PASS) (Rogers et al. 2010). We included fourteen RCTs in which five different instruments were used to measure functioning, of which only the SF-36 was validated in patients with late-life depression. This may have led to a lower sensitivity to detect subtle changes in functional status in older persons with late-life depression living in the community or with good physical health. In this regard, the WHODAS was recommended for research and clinical purposes, as well as the Late-Life Function and Disability Instrument (LLFDI) (Bingham et al. 2018; Karp et al. 2009).

Strengths and limitations

Although this review was performed in accordance with the highest scientific standards (Higgins et al. 2019), some limitations should be noted. First, to increase generalizability, studies on subgroups of depressed older persons were excluded from this review; for example depression in patients with cardiovascular diseases or in patients with cognitive impairment. The reverse of this decision is that we may have missed important information regarding interventions that target functional limitations in older adults with multimorbidity. Secondly, the data were too heterogeneous to perform a quantitative meta-analysis with respect to various levels of depressive symptoms, and the study populations had different characteristics, that is nursing home residents (Gitlin et al. 2013; Bondonelli et al. 2011), and community-dwelling depressed elderly (Breines et al. 2007; Choi et al. 2014, 2020; Gitlin et al. 2013; Huang et al. 2015b; Kiosses et al. 2010). Thirdly, because the topic of functional limitations is on the verge of nursing and medical care, we searched the primary database of medicine (PubMed) and the primary database of nursing (CINAHL). However, we may have missed articles that were only available through other databases. Lastly, most of the studies included in this review were conducted in primary care. Although this can be explained by the lack of attention given to functioning in specialized mental
health care, the results cannot be generalized to these populations.

Quality of studies
The majority of the studies presented with an unclear or high risk of bias. Only two collaborative-care studies showed a low risk of bias. The findings should therefore be weighted accordingly. This implies that the results from the physical exercise, medication, psychological treatment and the remaining collaborative-care studies were interpreted more cautiously.

Clinical relevance/future recommendations
The complexity of late-life antidepressant treatment is reflected in adverse course trajectories and low remission rates. The need for additional treatment options is high, and these additional treatments should consider old-age phenomena such as frailty and multimorbidity to improve functional recovery. Future studies should combine interventions within a collaborative-care approach. Collaborative care can be regarded as a complex intervention that contains several interacting components and demands for a different research approach than a straight forward RCT. Methodologies of complex intervention studies allow multiple interaction and synergetic components to be taken into account (Craig et al. 2008).

Validated measurement instruments of functional limitations are available, and nurses can use these measures broadly as an outcome of care and treatment in their daily work and in practice-oriented research.

The addition of a case manager is an important intervention to improve coordination of care in the medical, psychological and social domains. This is of utmost importance in an old-age population with comorbid mental and physical illnesses, especially because the prevalence of frailty and cognitive impairment is high in populations with multimorbidity, and two-way associations with functional status have been observed.

CONCLUSIONS
Targeting functional recovery as a treatment goal opens up new opportunities for increasing the success of antidepressant treatment in late-life depression. Collaborative-care interventions seem most promising for improvement of functional limitations, particularly in primary care and community-dwelling populations of older persons with depressed symptoms. However, there is a lack of evidence regarding studies in specialized mental health care. Most importantly, reduction of functional limitations as a treatment goal in old-age psychiatry aligns with the values of older persons.

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