

Subthreshold Depression Needs A Prime Time In Old Age Psychiatry? A Narrative Review Of Current Evidence

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Abstract: This study aims to carry out a narrative review, aiming to update the literature on subsyndromic depression (SD), which is the most prevalent depressive disorder in older adults, and no formal guidelines or consensus are dedicated to this topic. We carried out an electronic search for articles on SD. Relevant articles were retrieved from Pubmed, EMBASE and Web of Science using the search terms “subthreshold depression,” “prevalence,” “treatment” and “older adults” in several combinations. Original articles in English were included from inception to 1st March 2019. No clear consensus exists in the literature on its nosologic classification, diagnostic tools, causes, course, outcomes or management. SD diagnosis should base in depressive symptoms scales and DSM criteria. Treatment relies mainly on collaborative care and psychotherapy. SD is relevant in clinical practice and research in geriatric psychiatry. Given the negative outcomes and potential benefits of treatment, we recommend brief psychotherapy as first-line treatment and use of psychotropic agents in cases with greater severity and/or functional impairment in association with psychotherapy. SD can precede major depressive disorder, but it also may consist of a primary depressive disorder in older adults. Furthermore, adequate treatment of SD can prevent or reduce negative outcomes associated with depressive symptoms such as worsening of clinical comorbidities, loss of functionality, increased demand for health services, and increased mortality.

Keywords: subthreshold depression, prevalence, treatment, depressive symptoms, older adults

Introduction

Depressive disorders remain highly prevalent, resulting in disability, increased morbimortality and high health costs.¹ Depression encompasses emotional, cognitive, somatic, perceptual and behavioral symptoms despite the availability of a number of effective therapies, biological and otherwise. Almost 14% of individuals aged over 55 exhibit a depressive syndrome, of which only 2% are major depressive disorder (MDD).² On the other hand, many older persons affected by depression do not meet the criteria for an MDD (mostly according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5, or International Classification of Diseases 10th edition), having in fact subsyndromic or subthreshold depression (SD).

Defining SD poses a challenge owing to the heterogeneity of data on definitions for the condition. Conceptual definitions of SD are: 1) a disorder on its own, as considered by DSM-5; 2) a continuum with MDD; and 3) a combination of residual

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symptoms of depression. The most widely accepted definition in the scientific community, described in DSM-5, is the presence of two or more concurrent symptoms of depressive disorder, one of which is depressed mood, present most or all of the time for at least 2 weeks. The symptoms must cause dysfunction and negatively impact the individual's life and they may never have met the criteria for MDD or dysthymia.^{3,4}

A second approach centers on the notion that depressive symptoms considered subthreshold are part of the longitudinal continuum of MDD, i.e., it is a transient phenomenon, where each level of symptomatology is a representation of intensity, stage and severity of MDD.^{5,6} Lastly, the third group characterizes SD as residual symptoms of a depressive disorder, in other words, incomplete remission.⁷

SD is attracting increased attention of the scientific community, not only for its higher prevalence relative to MDD, but also owing to its impact on negative outcomes in later life.^{8–11} Older adults with SD are at greater risk of worsening clinical comorbidity, functional decline, greater demand for healthcare services and even increased mortality.^{9–11} This article provides a narrative review of the diagnostic concepts and associated clinical condition, risk factors, epidemiology, prognosis and treatment options for older patients with SD based on the best and updated evidence from the current literature.

Methods

This study involved a qualitative integrative review of the literature based on an electronic search for scientific articles focusing on SD. These articles were retrieved from the PubMed, EMBASE and Web of Science databases searched from inception through 1st March 2019 using the following medical subject heading [MeSH Terms] and search terms: (“subthreshold OR minor depression”) AND (“prevalence” OR “treatment” OR “older adults”). This initial search retrieved 770 articles for abstract analysis. In addition, the study included a manual review of related terms and citations drawn from the reference lists of the articles selected. Original articles in English were included without limits on year of publication.

Results

Epidemiology

The prevalence of SD is higher than for MDD and dysthymia, affecting around 10% of community-dwelling elderly,

20% of primary care patients, and up to 30% of hospitalized patients and nursing home residents.^{11–13} Moreover, 8–16% of older adults present clinically significant depressive symptoms (CSDS), a term also used in the literature to refer to SD.¹⁴

By comparison, MDD affects 1–4% of community-dwelling elderly, 5–10% of primary care patients and 10–12% of hospitalized older adults and nursing home residents.^{1,14} MDD rates can be as high as 37% in older ICU patients.⁶ In contrast, dysthymia affects around 2% of the elderly population.³ Similar rates can be found in middle-income countries. In a systematic review investigating the prevalence of depressive morbidity in Brazilian older adults, the authors found a rate of over 7% for MDD, 26% for CSDS and 3.3% for dysthymia.¹³ The Pietà study showed that 26.5% of community-dwelling individuals aged 75+ years have had CSDS.¹⁵

Risk Factors

The risk factors for the occurrence of SD are essentially the same as for depressive disorders. SD can be the cause or consequence of MDD, or both. The main factors established in the literature are given in [Box 1](#).^{11,16–18}

Diagnosis

Depressive disorders in older age have been under-diagnosed for several reasons: under-reporting by the patient or lack of active search by the health team, depressive picture different to younger adults, symptoms that resemble organic disturbances, polypharmacy, multimorbidity, depressive symptoms considered factors inherent to the aging process, stigma and fear of diagnosis of mental disorder. Diagnosing SD can be challenging as issues addressed during anamnesis such as depressed mood or loss of interest or pleasure can have a low impact on patient discourse and may be absent altogether.^{19–21}

Current and most commonly cited operational definitions of SD are 1) DSM-5 criteria for SD and/or 2) scoring above a cut-off of a screening tool for depression. Formal, structural and objective diagnoses of depressive disorders can be established using the International Classification of Diseases (ICD) and/or Diagnostic and Statistical Manual of Mental Disorders (DSM). The diagnostic criteria for SD according to the DSM-5 appear in [Box 2](#). Within the ICD-10 subthreshold depression is only classified for research purposes as a depressive disorder “not otherwise specified.” However, as the diagnostic criteria have not been clear, this classification is rarely used.

Box 1 Risk Factors For Subthreshold Depression

Female gender	Childhood poverty, abuse or neglect	Widow/widower, single and divorced
Low educational level	Poor socioeconomic level or social support or environment (both socially and/or economically)	Personal or family history of depression and/or other psychiatric disorder
Neurotic personality traits	Physical disability	Functional decline
Nursing home resident	Negative life events	Visual/hearing deficit
Advanced age	Cognitive decline	Loneliness
Insomnia	Clinical comorbidities e.g. Stroke, heart diseases, Parkinson's disease, chronic kidney disease, diabetes, cancer, etc.	Chronic uncontrolled pain

Box 2 Diagnostic Criteria For Subthreshold Depression According To DSM-5

"Depressed mood and at least one of the other eight symptoms of a Major Depressive episode, associated with clinically significant distress or deficit lasting at least 2 weeks, in individuals not meeting criteria for any other Depressive or Bipolar Disorder, and currently exhibiting no active or residual criteria for any Psychotic Disorder, and does not meet the criteria of mixed Anxiety or symptoms of Depressive Disorder."

By the way, minor depression is a diagnosis no longer classified in the DSM-5. Other validated instruments with established cut-off scores have shown good accuracy for detecting clinically relevant depressive symptoms. Therefore, these scales are useful, providing a comprehensive assessment of depressive symptomatology, covering a range of different symptoms and allowing a broader diagnosis of SD. The scales validated for SD are:²²

- Geriatric Depression Scale (GDS) – 30-item;^{23–25}
- Center for Epidemiologic Studies Depression Scale (CES-D) – 20-item;^{26–31}
- Hamilton Depression Rating Scale (HAM-D) – 17-item;³²
- Patient Health Questionnaire (PHQ-9);²¹
- EURO-D – 12 item.³³

Although depression scales are useful in clinical practice, we emphasized the paradox of not having an established cut-off for any of these instruments. Cut-off for clinically relevant depressive symptoms varies between countries, populations and settings (e.g., primary care, community-dwelling). Lavretsky and Kumar recommended a 12-point

cut-off in GDS 30 items for SD,²⁴ whereas Watson and colleagues determined a cut-off of 9 points.²⁵ The diagnosis of SD using the PHQ-9 is performed by 2 to 4 items, one of them must be anhedonia or sadness. We used the cut-off ≥ 10 points to define clinically significant depression and indicate the need for treatment. Lastly but not less important, an interview with the caregiver or family informant can be necessary in cases of depression with cognitive symptoms and/or under-reporting of depressive symptoms by the elder.²⁴

As seen, there is the possibility that the diagnosis can be made by scales of symptoms or categorical classifications. The criticism of this second modality, exemplified by the DSM, is that it was not specially adapted for depression among older adults, but only adequate to a certain extent in older age groups. The relatively low prevalence rates of major depression in seniors, compared with less severe variants of depressive disorders, may support this hypothesis.²⁶

CES-D cut-off scores showed the greatest reference variation among depression scales, varying from ≥ 16 points for DS^{26,29} with 100% sensitivity and 88% specificity, between 8 and 15^{27,31} and ≥ 9 points in other studies.^{28,30} In several European studies, especially the SHARE study, the EURO-D was used to measure depressive symptoms (used cut-off 4 points on a 12-item scale).³³ Highest percentages were observed in Southern Europe (35%), followed by Central and Eastern Europe (32%), Western Europe (26%) and lowest in Scandinavia (17%).³⁴ In the Netherlands, a cut-off of 16 points in CES-D used to identify clinically relevant depressive symptoms (Longitudinal Aging Study Amsterdam, LASA),³⁵ whereas in Italy a cut-off of 20 points identifies clinically relevant depressive

symptoms (InChianti study).³⁶ Finally, an interview with the caregiver or family informant can be necessary in cases of depression with cognitive symptoms and/or under-reporting of depressive symptoms by the elder.³⁷

We recommend that older people present depressive symptoms that include somatic symptoms, subjective complaints of memory and cognitive deficits with greater prevalence in relation to younger ones. This means that instruments or scales of symptoms that consider this particularity are often used to support the diagnosis.³⁸

However, one criticism of this is the possibility of considering a somatic symptom, when in reality it is a symptom of a current organic disease. For example, symptoms that commonly occur after an acute myocardial infarct, including fatigue, loss of energy, changes in sleep patterns and changes in appetite, they may be misinterpreted by health care professionals or researchers and misidentified.³⁹

Finally, we recommend that the diagnosis of SD be based on:

1. Diagnostic criteria (using a psychiatric interview to establish minor depression according to DSM-IV, or a depressive episode with insufficient symptoms according to DSM-5)
2. Scoring above a cut-off on validated screening scales.

Ideally, a combination of the two, like done in LASA,³⁵ i. e. minor depression is defined as a score above the cut-off on the CES-D (≥ 16) and not meeting the criteria for an MDD (based on the DIS).

Clinical Condition And Analysis Of Symptoms

Generally, SD can involve the same symptoms as established for MDD, as depicted in Box 3, with the differential

Box 3 Potential Depressive Symptoms In SD

Depressed mood and/or diminished interest or pleasure in usual activities	Feelings of worthlessness or excessive guilt
Decreased concentration and difficulty making decisions	Fatigue or loss of energy
Psychomotor retardation or agitation	Insomnia or Hypersomnia
Weight loss or gain and increase or decrease in appetite	Thoughts of death and suicidal ideation

being: the number, duration, severity and prevalence of symptoms, as well as the exclusion criteria.

Analysis of symptoms should take into account the specificities of depressive symptoms in older adults, as shown in Table 1 (Fogel et al, 2006; Kroenke, 2006; Pietrzak et al, 2013; Vaccaro et al, 2017).^{12,40-42}

As mentioned before, SD symptoms should be classified into three groups: the first group comprises prodromal symptoms of MDD; the second, residual symptoms of MDD; and lastly, in the third group, symptoms are regarded as inherent to SD. It is important to emphasize that for the first two hypotheses, although symptoms are similar, the conditions are different to the third.⁴³ Consequently, different types of intervention would be required (e.g., early psychotherapeutic intervention to prodromal MDD or watchful waiting strategy; change or addition of antidepressant or augmentation add-on therapy if residual symptoms; treatment of SD is discussed further). To make this distinction to both clinical and research settings, in-depth anamnesis is needed, besides an investigation of the history of previous depressive episodes that characterize MDD, a qualitative and quantitative assessment of symptoms present, the use of categorical scales and classifications, and previous and current use or otherwise of antidepressants, as well as serial reassessments of the patient. Furthermore, a time-window should be considered for which SD is prodromal of MDD (although prodromal can still be seen as a risk factor, but in that case not a causal risk factor).

An important aspect of the evolution of symptoms is differentiating which depressive symptoms or risk factors are most implicated in the progression of SD to MDD. Evidence in the literature is equivocal, but potentially important aspects are listed below.⁴⁴⁻⁴⁶

- Feelings of guilt or worthlessness;
- Poor concentration;
- Number of depressive symptoms;
- Family history of depression;
- Negative life events;
- Personality characteristics;
- Chronic diseases;
- Weight or appetite changes;
- Suicidal ideation;
- Sleep disturbance.

Rate Of Conversion From SD To MDD

The heterogeneity of studies on the subject, as outlined earlier, hampers the comparison of SD and MDD,

Table 1 Clinical Characteristics Of Depressive Symptoms In Older Adults

Symptoms	Clinical Characteristics
Affective symptoms	Depressed mood and loss of interest or pleasure may not have a major impact on the discourse of older patients. In clinical practice, it is not uncommon for older adults to be misdiagnosed with apathy instead of sadness and anhedonia.
Somatic symptoms	Often these symptoms are reported by older patients, and may be the sole or main complaint. These symptoms are often neglected because they may be associated with organic factors or patients become labelled "chronic complainers" by the health professional. Examples in clinical practice include reports of non-specific pain, fatigue, feeling of dyspnea and chest pain, dizziness, heaviness in the legs, malaise, among other symptoms.
Cognitive symptoms	A common complaint that may characterize dementia syndrome of depression, formerly called "pseudodementia" in moderate-to-severe depression. Cognitive complaints invariably involve memory and can be the reason for the medical visit.
Psychotic symptoms	These are not typical of SD.
Suicidal ideation/attempted suicide	Key differential between MDD and SD, where these symptoms are severe and characteristic of MDD.
Anxiety symptoms	Such symptoms are common in depressed patients. The two psychiatric comorbidities may be associated (depressive and anxiety disorder are often comorbid and diagnostic stability over time is limited)
Others	Social withdrawal, poor adherence to medications and medical visits, low self-care, abuse of alcohol or sedatives (e.g. benzodiazepines).

detracting from their results.⁴⁷ Notably, four studies showed that SD patients had persistent depressive symptoms during a 12-month follow-up, where one-third to a half of participants reported moderate functional impairment and at least 10–20% evolved to MDD.^{48–51} The CASPER study found SD to MDD conversion rates of 28–41% over 12 months,⁴⁶ whereas other studies suggested lower rates of between 10% and 20%.^{52,53} Some prospective studies indicated that 10% of adults with SD developed MDD every year, with similar rates confirmed among older adults.^{54–56}

A study conducted in the Netherlands through stepped intensive care in a randomized controlled design for the prevention of depression and anxiety in older adults with clinically relevant depressive symptoms (CESD ≥ 16) who did not meet the criteria for an MDD.⁵⁷ It showed that the intervention halved the incidence in 12 months of both depressive and anxious disorders.⁵⁷

Prognosis

In addition to not fulfilling the criteria for an MDD, SD should also not be associated with little, low or no impact on negative outcomes. In older adults, the depressive disturbance not only adds to the burden of other chronic diseases (e.g., angina, arthritis, asthma and diabetes) increasing morbimortality, but is also an important factor that exacerbates

existing comorbidities.^{58,59} Factors contributing to increased morbimortality are given in Box 4.^{3–7}

The literature clearly shows that depressive disorders increase mortality rates. A recent meta-analysis observed a relative risk of 1.58 associated with MDD and 1.33 with SD.⁶⁰ Both conditions were associated with significantly higher risk of mortality compared with non-depressed samples.⁶⁰ Although the risk of death is higher in MDD, the prevalence of the disorder is lower than for SD. Moreover, remission rates for SD are highly heterogeneous, ranging from 20% to 50% according to some authors.^{61–64}

Box 4 Negative Outcomes Associated With SD

Worse quality of life	Higher health costs	Functional decline
Increased risk of cognitive impairment and dementia	Worse evolution of clinical comorbidities	Greater demand for health services
Greater mortality	Greater hospitalization	Increased risk for major depression and dysthymia
Greater dependence on alcohol, illicit drugs and abuse of medications (e.g. sleeping pills, pain killers, etc.)	Emergence or exacerbation of other psychiatric disorders	Increased risk of suicide

Differential Diagnosis

Organic Diseases

In older patients, a symptom can often have more than one underlying cause. For example, a feeling of tiredness, fatigue and breathlessness can be secondary to a lung or heart disease, or may be of psychogenic origin. Therefore, investigating symptoms from both a psychiatric and somatic perspective is essential for the differential diagnosis of SD.

Older persons can have multiple comorbidities, yet similar symptoms. In addition, a psychiatric sign or symptom can be a prodromal state of somatic diseases such as Parkinson's disease, dementia syndromes, hypothyroidism, cancer, among others. Some examples of symptoms present in organic disturbances of older patients that can resemble depressive disorders are given in [Box 5](#).

The attending physician should assess symptoms and the clinical examination, order the pertinent laboratory tests and imaging scans to rule out clinical diseases, and determine whether the constellation of signs and symptoms indicates an organic syndrome. The physician should also be alert to any exaggeration, atypical feature in patient reports, and to whether there is response to therapy instituted, motivation and adherence to treatment. Finally, regular reassessment of the patient is essential to assess the spectrum of symptoms and check for emergence of new symptoms, given that the health professional may be dealing only with a clinical or psychiatric disease or both. In SD, watchful waiting is an essential first step in cases without functional decline or severity, and in case of persistent symptoms to institute treatment (see below).

Normal Sadness Inherent To The Human Condition

The context of old age is permeated by a host of different biological, psychological, social and financial changes. It is often hard to distinguish sadness secondary to these

changes from a depressive state. Health professionals need to differentiate a disorder of adjustment/coping (e.g., an elder who loses a family member or close friend, their retirement day, or being diagnosed with a serious illness) from a case of SD. Reassessment based on established diagnostic criteria, as well as subsequent monitoring of the negative impacts on the patient's life, are important to prevent under diagnosis of SD. Furthermore, accurate early diagnosis of SD is critical to avert unnecessary, costly and stigmatizing treatment in the future.

Treatment

The aim of treatment for SD is to reduce, or prevent, the negative outcomes associated with this depressive condition, and also to act as a powerful instrument for preventing MDD.⁶⁵ The benefits in the literature of SD treatment are well established and associated with improved prognosis. However, there is lack of consensus on the efficacy of different therapeutic strategies.^{66,67} We recommend following a checklist to improve the approach and interventions:

- (I) Clarity after assessment of patient, whether symptoms presented are residual after MDD, or exhibit symptomatology that does not fulfill criteria for MDD;
- (II) Assess symptoms presented in a qualitative and quantitative manner, determining the magnitude of the negative impact on the patient's life, such as on: professional, social, affective, personal and financial domains, and also the distress caused and decline in quality of life.
- (III) Conduct a full-personalized assessment for each patient to conclude which treatment will be most beneficial;
- (IV) Reassessing and monitoring the patient are also crucial.

Box 5 Organic Disturbances With Similar Symptomatology To Depressive Disorders

Cardiopulmonary diseases	Tiredness, fatigue, breathlessness, palpitation, weight loss, chest tightness and pain
Dyspeptic diseases	Chest pain, changes in appetite. Weight loss and distorted sense of taste.
Frailty syndrome	Fatigue, limb weakness, loss of appetite and weight loss
Oncologic diseases	Weakness, reduced appetite, weight loss, apathy and pains

“Watchful waiting”: this does not constitute a total absence of treatment, but entails systematic surveillance comprising assessment of symptoms, their course and impact. Although suggested in some guidelines, this may be insufficient, with questionable expectancy and risks inherent to negative outcomes.⁶⁸ Although not highly recommended in the literature, this approach may suit patients who have good social support, no personal or family history of depressive disorder, and that refuse pharmacological and/or psychotherapeutic treatment even after the risks and available treatment options have been explained.⁶⁸

“Patient preferences”: the literature on this topic is scarce and controversial. Some studies have failed to show favorable outcomes, whereas others report positive outcomes.^{69,70} In clinical practice, educating the patient about their illness and treatment options is of primary importance, so that both physician and patient can take a shared decision. A recent review showed benefits in terms of adherence, treatment satisfaction and outcomes.⁷¹

Psychotherapy: currently, psychological therapies, particularly brief ones, are the interventions showing the strongest evidence as first-line treatment.^{72,73} This approach is especially beneficial in older adults because it allows many psychic aspects and their functioning to be addressed. The CASPER study confirmed the merit of SD treatment in an older adults’ group enrolled in a structured program with psychological support and a behavioral approach.⁴⁶ The group was shown to have reduced depressive symptoms, as measured by the PHQ-9, after a four-month intervention compared to the group receiving usual treatment for depressive disorders.⁴⁶

Another important study was a meta-analysis that included seven studies and involved 700 individuals.⁷⁴ The risk of developing MDD in individuals that underwent the psychotherapeutic intervention was 30% lower. The study concluded that psychological treatment had significant effects and benefits on SD and that this intervention can reduce major depression or prevent its onset.

A meta-analysis of brief psychological therapies (typically 8 sessions or fewer) showed that cognitive behavior therapy (13 studies), problem-solving therapy (12 studies) and counselling (8 studies) all proved effective treatments of depression in primary care.⁷⁵

Phytotherapy: many patients seek phytotherapy alternatives. One of the most clinically popular is St. John’s Wort or *Hypericum perforatum*. However, the efficacy of phytotherapy is controversial, since most studies failed to confirm benefits over placebo in the treatment of MDD or SD.^{76,77}

Anti-depressants: Few studies have investigated the effects of pharmacological treatment in older adults with SD, where the majority of trials under-represent older people.^{78–80} A meta-analysis that included 6 clinical trials, with treatment using anti-depressants and placebo, found no advantages of the psychotropic agent over placebo.⁸¹ By contrast, another study comparing paroxetine with placebo showed the benefit of the anti-depressant in improving depressive symptoms and a positive impact on patients with more severe functional impairment.⁸²

The prescription of antidepressants is not recommended as first-line treatment or sole intervention for SD treatment.^{2,83–85} Despite scant literature on controlled trials of psychotropics in older patients, there is evidence of benefits of antidepressant use in SD patients who have more numerous and severe symptoms, and also in older patients with functional impairment and/or suicidal ideation.^{47,86,87}

Anti-depressants offer a number of advantages over psychotherapy. The former are immediately available and effects of treatment can be ascertained within a short timeframe (2–3 weeks). Additionally, psychotherapy may not be easily accessible and is often associated with waiting times, while assessing results also takes longer. Nevertheless, use of these drugs in older patients carries a higher risk of adverse events due to multiple medical comorbidities and drug–drug interactions in the case of polypharmacy.² The choice of pharmacological class should take into account the following factors:

- contraindication for medications;
- potential undesirable adverse effects, such as weight gain with tricyclic antidepressants in patients with metabolic syndrome, or adverse effects that benefit certain patients, such as when using mirtazapine to enhance appetite and sleepiness in patients with inverse symptomatology;
- access and cost of the treatment;
- previous personal or family outcomes after anti-depressant use.

In older adults, starting on lower doses with gradual increase is recommended, as is monitoring of side effects. In this age group, serotonin reuptake inhibitors (SSRIs) remain the first line of drug treatment.^{1,16}

Others: The following elements are also important in an integral approach:⁸⁸

- (a) adequate control of clinical comorbidities;

review of medications prescribed. A recent study highlighted depression as a potential adverse effects of prescription medications.⁸⁹ Main examples were gastrointestinal agents (omeprazole, ranitidine), anti-hypertensives (metoprolol, atenolol, enalapril), corticosteroids and analgesic agents. (tramadol, hydrocodone)

- (b) changes in lifestyle by giving up smoking and alcohol use, going on a healthy diet and engaging in physical activity;

- (c) interventions in social and family spheres to promote conflict resolution, social support and reintegration of the elder in different aspects of their life.

Conclusion

After ruling out organic causes and excluding the possibility of a diagnosis of MDD, dysthymia and coping/adjustment to negative life events, we recommend that patients be defined as SD. Despite the dearth of studies in the literature, disease management should be based on epidemiological evidence, negative outcomes and potential benefits of treatment.

We conclude that brief psychotherapy remains the first-line treatment approach, especially in frail older adults who are more vulnerable to multiple comorbidities. Psychotropic agents (especially SSRIs given the number of trials and clinical safety) prescribed in association with psychotherapy or as monotherapy can be recommended for patients with numerous or more severe symptoms and functional impairment. Further studies should explore the clinical course of older adults with depressive symptoms or SSD to better characterize this condition. Systematic reviews of current evidence are also needed to shed light on future study designs, especially to clinical trials.

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