



The Frail Depressed Patient: A Narrative Review on Treatment Challenges

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Abstract: Although the public importance of frailty is widely acknowledged by the World Health Organization, physical frailty is still largely neglected in geriatric mental health care. Firstly in this narrative review, we summarize the knowledge on the epidemiology of the association between depression and frailty, whereafter implications for treatment will be discussed. Even though frailty and depression have overlapping diagnostic criteria, epidemiological studies provide evidence for distinct constructs which are bidirectionally associated. Among depressed patients, frailty has predictive validity being associated with increased mortality rates and an exponentially higher fall risk due to antidepressants. Nonetheless, guidelines on the treatment of depression neither consider frailty for risk stratification nor for treatment selection. We argue that frailty assessment enables clinicians to better target the pharmacological and psychological treatment of depression as well as the need for interventions targeting primarily frailty, for instance, lifestyle interventions and reduction of poly-pharmacy. Applying a frailty informed framework of depression treatment studies included in a meta-analysis reveals that the benefit-harm ratio of antidepressants given to frail depressed patients can be questioned. Nonetheless, frail-depressed patients should not withhold antidepressants as formal studies are not available yet, but potential adverse effects should be closely monitored. Dopaminergic antidepressants might be preferable when slowness is a prominent clinical feature. Psychotherapy is an important alternative for pharmacological treatment, especially psychotherapeutic approaches within the movement of positive psychology, but this approach needs further study. Finally, geriatric rehabilitation, including physical exercise and nutritional advice, should also be considered. In this regard, targeting ageing-related abnormalities underlying frailty that may also be involved in late-life depression such as low-grade inflammation might be a promising target for future studies. The lack of treatment studies precludes firm recommendations, but more awareness for frailty in mental health care will open a plethora of alternative treatment options to be considered.

Keywords: frailty, depression, depressive disorder

Introduction

Depression is a debilitating condition in older adults. In the geriatric population, depression is associated with a lower level of wellbeing and quality of life, functional decline, cognitive impairment, premature nursing home admission, and even premature death by suicide or due to chronic somatic diseases.¹ These negative health consequences are associated with a depressive disorder according to criteria of diagnostic classification systems like the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) and the International Classification of Diseases (ICD-11) as well as to clinically relevant depressive symptoms (CRDS) measured by self-reported rating scales. Diagnosing depression may become increasingly difficult in later life as psychological symptoms such as low mood or feeling guilty may be expressed less explicitly, while the somatic-affective symptoms of depression symptoms may be difficult to differentiate from somatic multimorbidity.² Indeed, a recent review of depression rating scales found that overreliance on somatic items overestimates the prevalence of depression due to a higher prevalence of somatic diseases in later life.³ As outlined in this review, the prevalence of depression may also be overestimated among frail elderly.

Frailty is a condition of loss of homeostasis due to multiple system dysregulation yielding to a lower biological reserve against different forms of stressors.⁴ Frailty predicts future adverse health outcomes, like falls and fractures, physical disability, restricted activities of daily living, hospitalization, and in particular mortality.⁵ Although operational definitions of frailty are still a matter of debate, geriatric societies generally agree that biomedical frailty is clinically characterized by diminished strength, endurance, and a reduced physiologic function of several organ systems.⁶

Since symptoms and signs of frailty partly overlap with those of depression, the assessment of frailty in depression, or inversely, depression in frailty, is challenging. Nonetheless, unraveling this Gordian Knot systematically is critical to guide clinical practice and relevant regarding the progressively aging population worldwide. The objectives of this narrative review are twofold. First, we will summarize the knowledge on the epidemiology of the association between depression and frailty. We will build a case on why assessment of frailty within the context of depression is valid and clinically relevant, despite being mutual confounding. Second, we will formulate treatment rationales for depression in the presence of frailty based on the limited and often indirect evidence available.

Epidemiology Depression

The pooled prevalence rate of major depressive disorder was estimated at 1.8% for community-dwelling adults aged ≥ 55 years in one meta-analysis,⁷ and at 7.2% when combining community-dwelling and institutionalized older adults aged ≥ 75 years in another.⁸ These two meta-analyses found a pooled prevalence rates of clinically relevant depressive symptoms at 13.5% and 17.1%, respectively.^{7,8} When interpreting these numbers, we should keep in mind that clinically relevant depressive symptoms simply rely on a cut-off score of a (generally self-report) depression rating scale that weighs all symptoms and signs similarly. Thus, one can imagine that the presence of frailty may result in an overestimation of clinically relevant depressive symptoms in the oldest outpatients, although this has not been evaluated empirically yet. In contrast, depressive disorder can only be diagnosed when the core symptoms of depression, being a low mood or lack of interest (anhedonia), are present in addition to a minimum number of secondary depressive symptoms and when the patient is functionally impaired or significantly distressed. Classification systems (DSM-5, ICD-11) state that a symptom or sign only qualifies as a criterion for depression when this symptom or sign cannot be explained by an underlying somatic condition. This rule prevents diagnostic overlap between depressive disorder and frailty, but in clinical practice it can be very challenging, for instance, to assign a symptom like fatigue to either depression or frailty.

Frailty

Over the past two decades, a plethora of frailty assessment instruments has been developed based on different conceptual models of frailty. Within the geriatric literature there is an increasing preference to assess frailty either through the frailty phenotype criteria (Fried's criteria) or the frailty index.⁹ The frailty phenotype criteria is a syndromic approach in which a person is considered frail when at least three out of five criteria are met, ie, unwanted weight loss, muscle weakness, slowness, exhaustion, and a low activity level.¹⁰ According to the frailty index, which is based on the deficit accumulation model, a person is frail when at least 25% out of a list of ≥ 30 potential health deficits are present.¹¹ Since the frailty index is the proportion of potential health deficits that are present (theoretically ranging from 0 to 1), the frailty index is a dimensional scale assessing frailty severity which enables to evaluate frailty trajectories over time. Among community-dwelling older people aged ≥ 50 years, the prevalence of frailty has been estimated at 12% when operationalized according to the Fried criteria and at 24% when operationalized according to the frailty index (10).¹² Despite the different frailty operationalizations, all frailty definitions predict mortality over and above chronological age, the most widely used validity measure.

Frailty-Depression Association

About 10 years ago, epidemiologists had already pointed to similarities between many of the symptoms, consequences and risk factors for frailty and depression in older persons.¹³ Nonetheless, both constructs can be disentangled in large population-based cohort studies. Within the Baltimore Epidemiologic Catchment Area Study, confirmatory latent class analysis including the frailty phenotype criteria and the DSM-criteria for a depressive disorder supported the separation of frailty and depression

as distinct latent constructs, as opposed to a single construct.¹⁴ Notwithstanding, classifying people according to depression criteria (2.9% severe depressed, 19.4% mildly depressed, 77.7% not depressed) and to frailty criteria (21.1% frail, 78.9% not frail) resulted in highly overlapping classes, with a kappa value of 0.66 (95% CI: 0.57–0.74).¹⁴ Moreover, all persons classified as severely depressed were also classified as being frail.¹⁴ In the Health and Retirement Study, confirmatory factor analysis of either depression criteria or frailty criteria confirmed the presence of both dimensions.¹⁵ Nonetheless, depression severity highly correlated with frailty severity, regardless of whether based on frailty phenotype parameters ($\rho=0.68$) or the frailty index ($\rho=0.70$).¹⁵ When the factor analyses were repeated but accounted for shared symptoms, ie, depression criteria were allowed to load on the frailty dimension, and vice versa, the correlations weakened somewhat (frailty phenotype parameters: $\rho=0.45$; frailty index: $\rho=0.56$).¹⁵ Altogether, these initial findings show that frailty and depression are distinct but overlapping constructs that can be difficult to distinguish in clinical practice.

After these initial studies, meta-analyses of cross-sectional comorbidity rates have shown that among frail older adults, the pooled prevalence of depression was 38.6%, while inversely among depressed older persons the prevalence of frailty was 40.4%.¹⁶ The high comorbidity rates between frailty and depression may be partly explained by confounding, as only 3 of the 24 studies included had diagnosed depression according to formal diagnostic criteria.¹⁶ Within samples of depressed patients seeking mental health treatment, about one in four patients meet the frailty phenotype criteria for being frail.^{17,18} Nevertheless, another systematic review showed that the risk of being frail secondary to depression was consistent across study methodology and not conditional on specific depression criteria, frailty criteria, or covariate adjustment.¹⁹

Causality

Longitudinal studies investigating the causal relationship between depression and frailty in the literature are scarce ($n = 12$), as shown in Table 1.^{20–32}

The seven longitudinal studies with the highest methodological quality found that depressed older adults were approximately 2 to 3 times more likely to develop frailty than their non-depressed counterparts over a 3 to 5-year follow-up.^{20–26} These findings were independent of the exact operationalization of frailty, being mainly the frailty phenotype criteria, but also the frailty index²⁴ and other frailty instruments.^{22,24,25} Nonetheless, only one of these studies assessed depressive disorder based on a well-validated semi-structured diagnostic interview,²⁴ whereas the other studies only used screening scales. On the other hand, a large study with a 3-year follow-up found a significant dose-response relationship between severity of depressive symptoms and incidence of frailty (OR = 2.2 for severe symptoms, and OR = 1.3 for moderate symptoms), giving further credential for a causal association.²⁰

Acknowledging potential (long-term) side-effect of antidepressants, two of these studies also evaluated the association between antidepressant treatment and the onset of frailty.^{20,22} In the Women's Health Initiative Observational Study, the incidence of frailty was significantly higher among non-depressed antidepressant drug users (OR = 1.7 [95% CI: 1.4–2.1]), depressed patients not using antidepressants (OR = 2.1 [95% CI: 1.8–2.5]), and highest among depressed ones, antidepressant users (OR = 3.6 [95% CI: 2.4–5.5]) when compared to a reference group with no depression and no antidepressant drug use.²⁰ Furthermore, this risk differed between the type of antidepressants with an OR of 1.5 (95% CI: 1.2–2.0) for tricyclic agents, of 1.9 (95% CI: 1.4–1.5) for selective serotonin reuptake inhibitors (SSRIs), and 2.9 (95% CI: 1.9–4.7) for the combination of two or more agents, whereas duration of antidepressant drug use had no impact on the risk for frailty.²⁰ Among psychiatric outpatients, depression and monotherapy with SSRIs were significantly associated with frailty at baseline (OR = 2.8 [95% CI: 1.7–4.7]) as well as at a 12-month follow-up (OR = 2.8 [95% CI: 1.8–4.1]).²²

On the other hand, six studies have examined whether frail community-dwelling older adults are exposed to a higher risk of becoming depressed.^{27–32} Frail older adults were 2 to 4 times more likely to develop clinically significant depressive symptoms over a 2 to 4-year follow-up, although one study did not find any association.³¹ Studies were rather homogeneous regarding frailty and depression assessment as all five studies had assessed frailty according to the frailty phenotype criteria and all used a self-report depression screening scale (eg, Geriatric Depression Scale).^{27–29,31,32} Only one of these studies had a priori excluded antidepressant users to prevent reverse causation.²⁷

In summary, it can be concluded that frailty and depression are bidirectionally associated over time. The pathophysiologic mechanisms underlying this reciprocal association, however, remain complex and difficult to trace back to linear causality patterns (Figure 1). Most, if not all, physiological or molecular biomarkers associated with frailty have also

Table 1 Longitudinal Studies on Relationship Between Depression and Frailty

| Studies | Population: sample size, age (years), %women, Follow-up time | Prevalence of Frailty/ Depression | Incidence of Frailty/ Depression | Main findings |
|---|--|-----------------------------------|----------------------------------|---|
| Depression as a predictor of Frailty | | | | |
| Lahey et al 2012 ²¹ | 27,652, 65-79 years, 100% women, Follow-up= 3 years | _ / 6.5% | 14.9% / _ | Depressive symptoms and anti-depressant use were associated with frailty. Depressive symptom scores had higher risk for frailty (OR= 2.19, 95%CI= 1.86-2.59). |
| Paulson & Lichtenberg 2013 ²² | 1,361, ≥ 80 years, mean = 84.1 years, 100% women Follow-up= 4 years | 31.5% / 32.8% | 31.8% / 22% | Vascular depression and risk factors for cerebrovascular burden was a predictor of frailty. |
| Arahamian et al 2018 ²³ | 881, ≥ 60 years, mean = 81.6 years, 72.9% women Follow-up= 12 months | 37.7% / 18.7% | 9% / 4.7% | Combination of depression anti-depressant use (monotherapy with SSRI) was associated with frailty at baseline (OR= 2.82, 95%CI= 1.69 – 4.69) and over 12 months follow-up (OR= 2.75, 95%CI= 1.84 –4.11). |
| Zhang et al 2019 ²⁴ | 1,168, 70-84 years, mean = 74.9 years, 53.9% women Follow-up= 3 years | 5.9% / 8.9% | 9.3% / _ | Depressive symptoms were associated with increased risk of frailty (OR= 5.64, 95%CI= 2.85 – 11.14) at baseline, and incident frailty (OR= 2.79, 95% CI= 1.09 –7.10) over 3years follow-up. |
| Prina et al 2019 ²⁶ | 12,844, ≥ 65 years, 74.7 years, 64.5% women, Follow-up= 3-5 years | 12% / 26.9% | 27.4%-33% / _ | Depression was associated with a 59% increased hazard of incident frailty using the modified Fried phenotype and 19% for multidimensional frailty |
| Borges et al 2021 ²⁵ | 181, ≥ 60 years, mean = 73.2 years, 55.2% women Follow-up= 1 year | 37.5% / 25.4% | 18.6% / 31% | The presence of a depressive disorder was significantly associated with the onset of frailty (adjusted OR for FRAIL and FI-36: 3.07 [95% CI = 1.03–9.17] and 3.76 [95% CI = 1.09–12.97], respectively. |
| Da mata et al 2021 ²⁶ | 1,109, 60-96 years, mean = 72 years, 61.1% women Follow-up= 3.8 years | _ / 12.8% | 12.6% / _ | Older adults with depressive symptoms presented a 29% greater risk of developing frailty (IRR = 1.29; 95%CI= 1.26 –1.32). However, the adjusted model showed not to be statistically significant (IRR = 1.21; 95%CI= 0.62 –2.36) (P = 0.772). |
| Frailty as a predictor of Depression | | | | |
| Feng et al 2014 ²⁷ | 1,827, ≥ 55 years, mean = 65.9 years, 64.3% women Follow-up= 4 years | 2.5% / 11.4% | _ / 2.4% | Frailty more than doubled risk of depression (OR= 2.36, 95%CI= 1.08 – 5.15). |
| Makizako et al 2015 ²⁸ | 3,025, ≥ 65 years, mean = 71.4 years, 50.3% women Follow-up= 15 months | _ / _ | _ / 7.5% | Frailty was an independent predictor of depressive symptoms (OR= 1.86, 95%CI= 1.05 – 3.28). |
| Collard et al 2015 ²⁹ | 888, ≥ 65 years, mean = 73.4 years, 56.3% women Follow-up= 9 years | 21.3% / 6.8% | _ / 30.6% | Frail older adults had 26% higher risk of depression (RR=1.26, 95%CI= 1.09–1.45) and lower likelihood of remission (RR= 0.72, 95%CI= 0.58 – 0.91). |
| Collard et al 2017 ³⁰ | 280, ≥ 60 years, mean = 70.7 years, 66.1% women Follow-up= 2 years | 26.4% / 100% | _ / _ | Frailty was associated with greater severity of depressive disorder. Reduction of depressive symptoms was greater among frail older adults. |

(Continued)

Table I (Continued).

| | | | | |
|-----------------------------------|--|-------------|----------|---|
| Veronese et al 2017 ³¹ | 4,077, ≥ 60 years (60 – 90 years), mean= 70.9 years, 53% women Follow-up= 2 years | 6.3% / _ | _ / 8.8% | In a logistic regression analysis, adjusted for 18 potential confounders, pre-frailty (OR = 0.89; 95% CI= 0.54–1.46; p = 0.64) and frailty (OR = 1.22; 95% CI= 0.90–1.64; p = 0.21) did not predict the onset of depression at follow-up. Among the criteria included in the frailty definition, only slow gait speed (OR = 1.82; 95% CI= 1.00–3.32; p = 0.05) appeared to predict a higher risk of depression. |
| Chu et al 2020 ³² | 1,264, 70-87 years, mean = 76.7 years, 52.7% women Follow-up= 18 months | 9.0%/ 10.6% | _ / _ | Frailty was associated with depressive symptoms at baseline (OR = 4.64, 95%CI= 2.49 – 8.66), and over 18 months follow-up (OR = 2.12, 95%CI= 1.17 – 3.83). |

been linked to depressive disorder in middle-aged and older persons, in particular immune-metabolic dysregulation, autonomic nervous system dysregulation, dopamine depletion, and mitochondrial dysfunction.^{33,34} Also, these phenomena seem to be related to complex bidirectional interactions, which are beyond the scope of the present review.

Predictive Validity

Overlapping diagnostic criteria for frailty and depression as well as shared underlying pathophysiological mechanism (Figure 1), may question the predictive validity of frailty in late-life depression. This might be especially true acknowledging the huge amount of cohort studies showing that depression itself is a risk factor for premature mortality³⁵ since frailty has been introduced in geriatric medicine to identify patients at increased risk of adverse health effects, with premature death as the most important validator. Moreover, the prospective association of frailty with mortality differs between disease clusters, with the highest predictive value among patients with pulmonary and heart diseases^{36,37} and lowest predictive value for patients with neuropsychiatric disorders.^{37,38} Yet, using data of the Netherlands Study of

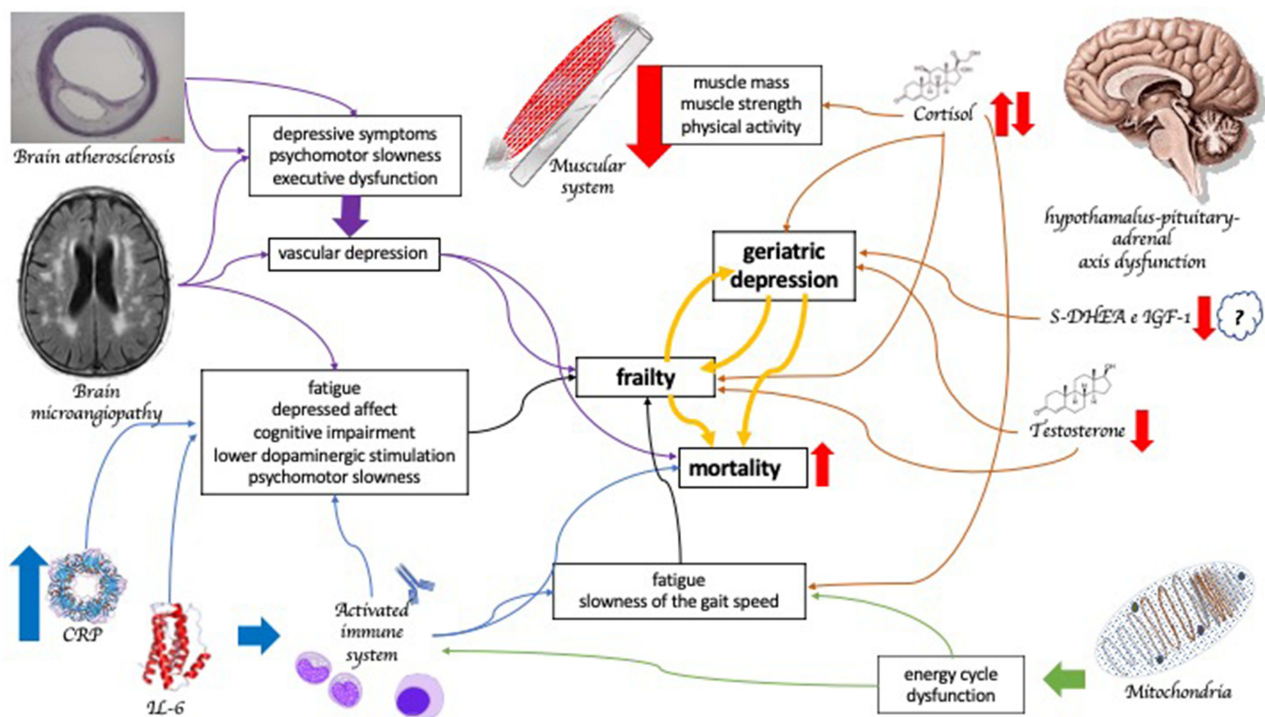


Figure 1 The pathophysiological interaction between geriatric depression and frailty. Both conditions present an interplay in immune-metabolic dysregulation, autonomic nervous system dysregulation, dopamine depletion due to frontostriatal network impairment, and mitochondrial dysfunction.

Depression in Older persons (NESDO), we showed that frailty at baseline was highly predictive of premature mortality among depressed older patients, irrespective whether frailty was operationalized according to the frailty phenotype criteria³⁹ or the deficits accumulation model underlying the frailty index.⁴⁰ In sum, these studies support the (predictive) validity of frailty assessment in depression and thus for risk stratification in geriatric mental health care. In the second part of this review, implications for treatment will be discussed.

Pharmacological Treatment

Pharmacological treatment of depressive disorder is less favorable among older patients compared to their younger counterparts. First, a meta-analysis of randomized controlled trials on the efficacy of antidepressants has shown that these agents are less effective in older compared to younger patients.⁴¹ Moreover, an observational study including 1042 depressed patients aged 18–88 years showed that a higher age was associated with a more chronic course of depression, prolonged time to remission, and higher symptom severity over a two-year follow-up.⁴² Finally, pooled results of 34 randomized controlled trials including only depressed older patients aged ≥ 60 years showed that the efficacy of antidepressants decreases with increasing age.⁴³

We postulate that these findings may be explained by an increasing prevalence of frailty with age. A systematic review of 27 randomized clinical trials (RCTs) evaluating the effectiveness of antidepressants for older adults has evaluated to what extent geriatric characteristics, such as frailty, multimorbidity, disability, malnutrition, and cognitive impairment were considered in the study design.⁴⁴ Remarkably, frailty and malnutrition have never been considered. Furthermore, when considered, most geriatric characteristics were used as an exclusion criterion. To get hard evidence on the impact of frailty on treatment outcome, RCTs should perform randomization stratified in the presence of frailty. Due to the paucity of knowledge on the impact of frailty in the treatment of depression, the results of another meta-analysis on antidepressants for the treatment of late-life depression have been subjected to a frailty-informed framework to consider how the evidence could be applied to frailty.⁴⁵ This frailty-informed framework estimates to what extent frailty might have affected the results of the meta-analysis by interdisciplinary discussions regarding 1) characteristics of the trial population; 2) outcomes; 3) timeline for benefit; 4) harms; and 5) other relevant evidence.^{46,47} The authors concluded that frail older adults might be overtreated with antidepressants with little to no benefit at the cost of highly relevant side-effects for frail older persons and thus advocated “less is more” in management of depressed frail patients. According to that conclusion, we observed that SSRI monotherapy and depression were independently associated with a higher risk of falling during a one-year follow-up among 811 geriatric outpatients.⁴⁸ Interestingly, the risk of falling related to SSRI usage and frailty interacted significantly giving rise to an exponential increase in fall risk.⁴⁸

To our knowledge, only two observational studies that have examined prospectively the impact of frailty on the course of depression among depressed older patients referred to mental health treatment. In both studies, frailty was assessed according to the frailty phenotype criteria¹⁰ and both confirmed the presence of a depressive disorder at baseline with a diagnostic interview and examined the course of depressive symptoms over time.^{30,49} Among 285 depressed patients, those meeting the frailty phenotype criteria for frailty, 46.6% remitted according to DSM-criteria, which was comparable to a remission rate of 48.5% for pre-frail patients, but significantly less than 69.4% among robust patients.³⁰ Interestingly, frailty was associated with significantly greater improvement of depressive symptom severity over time (due to higher baseline levels of these symptoms). In other words, frail depressed patients greatly improved with respect to depressive symptoms, but after two years they still suffered from a higher level of (residual?) depressive symptoms compared to their non-frail depressed counterparts.³⁰ These findings were replicated in a smaller American study including 100 depressed patients.⁴⁹ An intriguing question that remains unanswered by these empirical data is how we should classify these patients at follow-up. Should we consider them as suffering from residual depressive symptoms? In that case, switching or augmenting antidepressants should be considered for further improvement and/or relapse prevention. Or should we consider them as frail primarily? In that case, frailty management or geriatric rehabilitation may be more appropriate and the use of polypharmacy and/or psychotropic drug should be prevented (as discussed below). In other words, both diagnostic perspectives refer to different treatment guidelines applied in different health-care settings⁴ and misclassifying frailty for depression or the other way around may place patients at risk of inappropriate treatment.

Due to the lack of antidepressant treatment studies among frail depressed patients, we can only recommend being critical whether initiating an antidepressant is really needed as well as paying extra attention to the monitoring of side-effects. Regarding choices for specific antidepressants, antidepressants targeting slowness and/or exhaustion more specifically might be preferred based on the clinical profile of the frail depressed patient. In this regard, dopaminergic antidepressants may be preferred. Indeed, pharmacologic augmentation of dopaminergic neurotransmission, such as dopamine agonists (ie, L-dopa or pramipexole) as well as stimulants (ie, methylphenidate) have been shown to improve slowing and depressive symptoms in late life depression.^{50–52}

Psychological Treatment

In contrast to a decreasing efficacy of antidepressants with increasing age, age has not been identified consistently as an effect modifier for the outcome of psychological treatment of depression. A large meta-analysis of the effectiveness of psychotherapy in different age groups was not able to demonstrate clinically relevant differences between middle-aged (≥ 24 –55 years), older (≥ 55 –75 years), and very old (75 years and older) patients but firm conclusions were limited due to large heterogeneity between trials and methodological shortcomings.⁵³ Although circumstantial, these findings fit with two meta-analyses that demonstrated good effectiveness of psychotherapy for depression in patients with somatic comorbidity.^{54,55} Nonetheless, observational data of 28,498 patients referred for psychotherapy showed that patients with long-term somatic illnesses had similar outcomes compared to those without somatic comorbidity, excepted those with musculoskeletal condition, chronic obstructive pulmonary disease, and diabetes, considering that cases with somatic comorbidity needed more therapy sessions to achieve the same results.^{56,57}

One explanation for the lack of an age-effect might be that psychotherapy studies often include persons with clinically relevant depressive symptoms irrespective of whether these persons meet the diagnostic criteria for a depressive disorder. These milder subtypes of depression can often be considered as a psychological response to a stressor – an age-related somatic disease, for example. Psychotherapy may thus effectively target these maladaptive psychological responses irrespective of age. Pharmacological studies more often apply stringent diagnostic inclusion criteria that pertain to dysfunctional brain circuitries less amenable to change in later life. Regardless of whether these explanations hold true, the empirical results suggest that older persons that do not meet the criteria of a depressive disorder but pass the cut-off for clinically relevant depressive symptoms due to an emotional response to their frailty status may still benefit from a psychotherapeutic approach. Moreover, most older patients prefer psychotherapy over antidepressant drug use.^{57,58}

Psychological aspects of frailty have received little attention in the literature, while available studies show that frailty is associated with low levels of well-being.⁵⁹ Due to the gradual and slow progression of frailty, frail older adults often face a lower quality of life for longer periods of time compared to patients with terminal illnesses. This decline in subjective well-being, life satisfaction, and overall health is more closely related to the distance from death than to chronological age and generally starts around 3–5 years before death.^{60,61} When facing the latest stages of life, well-being becomes much more important from a patient's perspective than the actual level of functioning. The very gradual transition from fitness to frailty is often accompanied by maladaptive psychological responses.^{59,62} To this end, it has been argued that prevention programs aimed at reducing frailty should also evaluate meaning in life and include meaningful activities to ameliorate social connectedness.⁶³ Psychological therapies, however, have never been studied in frail people to improve their quality of life and well-being. In geriatric medicine, psychosocial interventions are often advised, but generally directed to primary health care for implementation. General practitioners often prioritize physical health over mental health in frail patients due to limited time in consultations and the complexity of their needs.⁶⁴ As a result, frail patients will not receive psychotherapy or will be coached by nurses or mental health workers who often lack formal psychotherapy skills.

In our opinion, especially the movement of positive psychology, such as acceptance and commitment therapy (ACT), mindfulness-based stress reduction (MBSR), and life review, might be relevant to target maladaptive (psychological) responses to frailty as outlined below.

Acceptance and Commitment Therapy (ACT) is a promising psychotherapy to improve quality of life and well-being of frail older adults since ACT focuses on possibilities acknowledging the presence of losses and handicaps. The objective of ACT is not to eliminate difficult or unpleasant feelings, which are inevitable for frail persons, but rather to stimulate them to embrace what life brings them now and to move toward valued behavior.⁶⁵ ACT helps people to

clarify their personal values, stimulates them to take the appropriate actions, and also to increase meaning in their life within their possibilities.⁶⁶ The evidence of ACT is well established for the treatment of several psychiatric disorders.^{67,68} Moreover, ACT is increasingly being applied as a psychological intervention to improve functioning, well-being, and quality of life for people living with chronic somatic conditions, like diabetes, cancer, and chronic pain.^{69–71} Among people with chronic pain, older patients were more likely to respond to ACT whereas younger patients better responded to cognitive therapy,⁷² an indirect argument to favor ACT above cognitive therapy for frail older adults.

Mindfulness is the process of paying attention to the present moment in a receptive and non-judgmental attitude.⁷³ Several studies have shown that mindfulness protects people from the well-known harmful effects of stress on mental health⁷⁴ and might even dampen cellular aging.⁷⁵ Mindfulness-Based Stress Reduction (MBSR) and mindfulness practice can cultivate an awareness of life, moment by moment, and supports an older person to face frailty and physical losses with presence and equanimity. While MBSR has been developed as a specific therapy protocol, training in mindfulness is also part of most ACT protocols. Two systematic reviews showed that MBSR is acceptable and feasible for older adults for the treatment of stress-related conditions, even though its effectiveness in later life is still debated due to methodological flaws of the studies conducted thus far.^{76,77} Moreover, the impact of MBSR on mental well-being in frail older persons specifically has not been examined yet.

Life Review Therapy has been conceptualized as a natural process of recalling, evaluating, and analyzing past experiences to achieve a more profound self-concept in people who approach the end of their life.⁷⁸ In Life Review Therapy, an individual's forgotten, but influential, experiences are revealed; their negative experiences are analyzed logically; and their positive experiences are discussed to make them feel useful and important again.⁷⁹ Life Review Therapy addresses subjects that, due to unresolved conflicts, are hard to analyze by oneself without feeling upset, disgusted, or guilty. An RCT comparing Life Review Therapy to usual care among 74 frail nursing home residents found a significantly larger improvement of life satisfaction compared to usual care, but no impact on personal meaning.⁸⁰

Frailty Management in Depression

In the previous sections on treatment of frail depressed patients, we focus on the potential adaptation of traditional mental health treatment guidelines. But what can be learned from geriatric frailty prevention and treatment programs?

Multidomain intervention programs, including physical exercise, nutritional intervention, and psychosocial support, are generally advocated to prevent, stabilize, or even reverse physical frailty.⁸¹ The evidence, however, is only sufficient for physical exercise to implement in clinical practice, with some evidence for combined exercise-nutrition interventions.⁸² This knowledge suggests that psychiatric treatment should be enriched with physical exercise and a nutritional advice to target physical frailty among older patients in specialized mental health care. This strategy might be relevant and effective for several reasons. First, psychiatric patients generally have an unfavorable lifestyle compared to the general population, which is relatively sedentary, with less physical activity, a less healthy diet, and less social contact. Therefore, frailty management may achieve even greater benefit in psychiatric patients compared to the general population. Second, patients with psychiatric disorders are often excluded from community or primary care-based life-style interventions and if not, often refuse participation. Implementing these programs within mental health treatment may overcome some barriers these patients face when offering life-style interventions in primary care or their neighborhood. Third, meta-analyses have shown that physical exercise also reduces depressive symptoms in later life with a small to moderate effect-size.^{83,84} Actually, a *win-win* situation for frail depressed patients. The implementation of physical exercise can be initiated in home care, together with training of a family member or caregiver, increasing the cost-effectiveness of the intervention.⁸⁵ Generally, this type of intervention is quickly implemented and seen as favorable by patients and families.⁸⁵ In addition, interventions of this type and with low resistive load (initially) are shown to be favorable and effective in patients with cognitive impairment associated with frailty, which constitutes an additional barrier to the improvement of frail patients with depression.^{86,87} Cognitive impairment should also be addressed in the treatment plan of depressed frail patients, as impaired cognition could mediate adverse outcomes.⁸⁸

In addition to the clinical approach of frailty, targeting shared pathophysiological mechanisms (Figure 1) underlying frailty and depression have also been proposed as promising avenues for future research, especially mitochondrial

dysfunction, dopamine depletion, and inflammation.³⁴ A recent systematic review found that several anti-inflammatory agents can improve the effect of antidepressants.⁹¹ In this line, a potential agent would be metformin due to its broad action in several pathways involved in the pathophysiology of frailty and depression. Some studies are under development.^{89,90} Unfortunately, data were too limited to specify which patients profit most from this strategy.

Conclusion

Although the public importance of frailty is widely acknowledged by the World Health Organization,⁹² physical frailty is still largely neglected in geriatric mental health care.⁴⁴ This should be changed since depressed older patients are two to four times more likely to be physically frail compared to the general population,^{16,29} and functional recovering is achieved only in the minority (~20%) of cases.⁹³ As pointed out in this review, treatment studies on frail depressed patients are lacking. In clinical practice, comorbidity between frailty and depression can be quite complex, and physical frailty can be detected using self-reported questionnaires or simple physical maneuvers.^{94,95} Overlap between diagnostic criteria may easily result in overdiagnosing depression among frail elderly, but also depressed older patients might be considered “pseudo-frail” when exhausted and slowed down by their depression. Nonetheless, we hope that this review may stimulate the awareness of frailty and its detection in mental health care and may stimulate collaboration between health-care settings to allow clinicians to consider the plethora of potential treatment options available, including their potential benefits and pitfalls for the individual patient.

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Disclosure

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