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Treatment-resistant Late-life Depression: Challenges and Perspectives

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Abstract: The current Review article provides a narrative review about the neurobiological underpinnings and treatment of treatment resistant late-life depression (TRLLD). The manuscript focuses on therapeutic targets of late-life depression, which include pharmacological, psychological, biophysical and exercise treatment approaches. Therefore, we summarize available evidences on that kind of therapies for patients suffering from late-life depression. The search for evidences of therapeutic options of late-life depression were done using searching websites as "pubmed", and using the searching terms "depression", "late-life depression", "treatment", "biophysical therapy", "exercise therapy", "pharmacological therapy" and "psychological therapy". To the end, we summarize and discuss current data, providing some directions for further research.

Treatment recommendations for elderly depressive patients favour a multimodal approach, containing psychological, pharmacological and secondary biophysical therapeutic options. Particularly, a combination of psychotherapy and antidepressant medication reflects the best therapeutic option. However, mostly accepted and used is the pharmacological treatment although evidence suggests that the drug therapy is not as effective as it is in younger depressive patients. Further studies employing larger samples and longer follow-up periods are necessary and may focus on comparability of study designs and involve novel approaches to establish the validity and reliability of multimodal treatment programs.

Keywords: Antidepressants, electroconvulsive therapy, late-life depression, psychotherapy, review, treatment-resistant.

1. INTRODUCTION

Major Depression Disorder (MDD) is among the most debilitating diseases worldwide with highest reductions in disability adjusted years of life among all human diseases (1). MDD is a high prevalent disorder characterized by episodes of persistent depressed mood or loss or interest or pleasure [1]. Depressive episodes may include an array of heterogeneous symptoms, including disturbed sleep, weight changes, psychomotor agitation or retardation, lack of concentration, fatigue or loss of energy, feelings of worthlessness and guilt and suicidal ideation [1]. Lifetime prevalence of major depressive disorder (MDD) is up to 20% [2]. Therefore, there is a need for developmenting and evaluating treatment options for mood disorders.

In the elderly, depression is the second most common psychiatric disorder [3]. The long-term course of depression has been hallmarked as being highly recurrent, often leading to considerable cost for the patient and society [4-6]. Age has been pointed as one important variable associated with deterioration, with studies showing a poorer course of MDD in elderly patients comparatively with adults [7]. Distinct rates of recurrence were reported by studies, with differences among studies varying according to the follow span (*i.e.*, the longer the individual follow up, the higher the number of recurrences). Studies with primary care patients reported recurrences between 33% and 65% over three to 23 years [6, 8, 9]. Studies have reported a rate of unremitting course from 10 to 17% among MDD subjects [6, 10-12]. Predictors of poorer response may include physical and sexual abuse in childhood [13], age at onset [14], lower education and number of previous recurrences and day of untreated episodes [12, 15]. Additionally, personality disorder diagnosis may predict a further episode, while somatoform disorders predict time to recurrence [8].

Depression in the elderly challenges the available treatment options, as elderly depressive patients – together with depressive symptoms" - commonly suffer from disability, functional decline, diminished quality of life as well as mortality from comorbid medical conditions or suicide [16]. Following these facts, elderly depressive patients have more demands on caregivers, an increased service utilization and special need for treatment strategies [16]. In the group of elderly depressive patients, treatment resistant late-life depression (TRLLD) is a special group of patients, with special therapeutic targets and special need. A common characteristic of antidepressant pharmacotherapy is that a substantial proportion of patients may not show appropriate therapy response or recovery [17, 18]. Clinical response is

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usually defined as improvement by at least 50% on clinical rating scales such as the HAM-D (Hamilton Depression Scale) [19]. However, even after several consecutive steps of therapy escalation, the cumulative remission rate in depressed patients (irrespective of age) did not surpass 67% in the STAR*D study [18]. Treatment-resistant depression is a common clinical problem, and not limited to the elderly. However, the number of treatment-resistant elderly depressive patients is about one-third of the elderly depressed patients [20].

While many different definitions and algorithmic approaches to therapy refractory depression (TRD) or treatment-resistant late-life depression ("TRLLD") exist [21], we will provide data of trials in older depressed adults (> 65 years; "late-life depression" [LLD]), with or without adequately responding to any initial antidepressant therapy ("TRLLD" or "TRD"). Throughout the current manuscript, we followed the diction of the authors when picturing the targets and findings and using the terms "TRLLD" or "TRD" (treatment-resistant late-life depression) and "LLD" (late-life depression) or "elderly depressive patients" used by authors.

This review represents a narrative review about the neurobiological underpinnings and treatment targets of late-life (LLD) or treatment resistant late-life depression (TRLLD). The search for evidences of therapeutic options of late-life depression were done using searching websites as "pubmed", and using the searching terms "depression", "late-life depression", "treatment", "biophysical therapy", "exercise therapy", "pharmacological therapy" and "psychological therapy". The following chapters include "Symptomatology & course of illness of late-life depression", "disease model of late-life depression", "therapeutic targets of late-life depression" and ends with a discussion of current and new approaches.

2. DISEASE MODEL OF LATE-LIFE DEPRESSION

Nowadays, depression is generally seen as the result of the psychobiological final common pathway [22]. This multifactorial 'final common pathway model' integrates psychodynamic, socio-behavioral, and neurobiological research into a clinically meaningful framework. The authors conceptualized depression as the feedback interaction of three sets of variables at chemical, experiential, and behavioral levels with the diencephalon serving as the field of action. The psycho-biological disposition includes genetic and biographical components and is formed by personality traits. However, the genetic load seems to be of less impact in depression with age at onset older than 65 years [23].

2.1. Psychological Theories

Several models for the development of depression have been discussed. Aaron Beck developed the theory that depression results from a 'cognitive triad' of negative thinking patterns or 'schemes', about oneself, one's future and the world [24]. Besides that, cognitive ('learned helplessness' [25]) and various behavioral models of depression have been proposed (*e.g.* [26, 27]).

Only few psychological models have specifically been developed for depression in the elderly: The model of 'individual opportunities' [28] includes four areas: activities, decisions and control, as well as interaction and recognition. However, most disease models were adjusted for late-life depression. While late-life per se is not a risk factor for depression, there are several predisposing factors, which are – partly – correlated with older age [29]:

- Female gender (male:female 0,3:0,7)
- Personality (avoidant, obsessive-compulsive, introverted personality traits)
- Previous depression episodes
- Severe physical illness
- Spouse's death and divorce

More than 50% of all patients with late-life depression have significant life-events, which are in (close) temporal relation with the depressive episode. It is plausible that these life events, in particular physical illness, may trigger depressive episodes [30]. Loneliness and lack of life satisfaction also seem to be relevant risk factors for depression [31], but not educational level [32]. Physical stressors are determined by an increasing incidence of physical illnesses. All these factors finally lead to the common patho-physiological final pathway with changes in neuro-biological systems, resulting in the clinical symptomatology of depression.

2.2. Biological Theories

Although the diagnosis of LLD is based on phenomenological observations, LLD is known to have a huge biological basis [33]. Biological changes underlying MDD may stem from neural circuitry and neuroendocrine deregulation [34], probably resulting from genetic vulnerability, which might interact with stress promoting lesions and epigenetic modifications along the life cycle [35]. Among the elderly people, MDD may be associated with brain changes due to the ageing process [23]. A large body of evidence has identified several neuroanatomical changes in MDD subjects, with considerable variation across studies [36]. Brain structural abnormalities in the cingulum, in the dorsolateral prefrontal cortex as well as in the amygdala are known to be involved in the occurrence and cause of depressive symptoms. Vascular lesions, often recognized as white matter (WM) hyperintensities, have been associated with depressive onset and symptoms, leading to the hypothesis of a "vascular depression model" [37]. Depressive symptoms precede memory decline in late life [38] and late-life depression is associated with cognitive deficits [39]. A depression-associated loss of neurons in the hippocampus [40] might be explained by increased stress responsiveness of the HPA (hypothalamic-pituitary-adrenal)–axis [41].

Regarding LLD, this form of mood disorder is associated with higher risk for all-cause dementia, but was a significantly higher risk for vascular dementia than for Alzheimer's disease [42]. Diniz and colleagues [43] investigated in n = 80 elderly depressive patients potential associations between cognitive impairment and proteomics as well as structural imaging markers. The group of

participants have been divided into LLD with MCI (mild cognitive impairment) (LLD + MCC) and without (LLD). Their findings revealed that cognitive deficits in LLD are related with greater cerebrovascular disease, together with abnormalities in immune-inflammatory control, cell survival, intracellular signaling, protein and lipid homeostasis, and clotting processes [43].

Furthermore, there are several other changes in both, gray and white matter of the brain [44]. Mettenburg *et al*. [45] reported increased radial diffusivity in specific regions, suggesting underlying myelin injury. A possible mechanism for underlying myelin injury is chronic white matter ischemia related to intrinsic cerebrovascular disease. Interestingly, there are hints, that vascular risk factors may reduce the depressive effect of stressful life events. However, vascular risk factors cannot be interpreted within the stress-vulnerability model; they represent an alternative pathway to depression [46].

There are several neurobiological factors involved in the etiology of late-life depression. Firstly, the hypothalamic-pituitary-adrenal axis is of particular relevance for the development of depression. On the microcellular level, structural and functional changes in the cell and in the brain might be elicited by stress. Stress triggers a chain of events in the HPA-axis which eventually lead to increased serum blood cortisol, decreased BDNF (brain-derived neurotrophic factor), increased IL10 (interleukin) and alpha TNF (tumor necrosis factor) levels, and decreased IL6 (cytokines) [47]. The cytokines are liberated by the microglia, and this is leads to neuronal apoptosis [48, 49]. This inflammatory reaction stands as a key to the maintenance and worsening of depressive symptoms and changes in the brain structure and function in MDD patients.

Activation of the HPA axis is one of the most comprehensively documented changes in major depression [50]. Both, centrally released CRH (cortisol releasing hormone) and increased levels of cortisol may contribute to the symptoms of depression. The dexamethasone/CRH test is one of the most reliable neuroendocrine function tests for HPA system dysregulation in depression. Elevated cortisol responses to the combined DEX/CRH test were consistently observed in patients suffering from MDD [51, 52]. It was shown that in the long-term course of depression the HPA system deterioration increases in parallel with the number of previous episodes [53].

Among neurotropic factors, BDNF appears to be a particular relevant factor for mood disorders and associated cognitive dysfunction [54]. Several recent meta-analyses revealed that serum BDNF levels in MDD patients are reduced compared with healthy controls [55, 56] and return to comparable levels as the control group after antidepressant therapy [57]. A study by Diniz and colleagues [58] including n = 160 participants, revealed a significant effect of time on BDNF in 2 years follow up measures, with no effect of donepezil treatment on BDNF level. Another neurotrophic factor, glia cell line-derived neurotrophic factor (GDNF) was reduced compared with healthy controls and GDNF levels were associated with the severity of depression, specifically in elderly patients with MDD [59].

There is evidence that the noradrenergic and in particular the serotonergic system are involved in the development of depression. Cross-talk between BDNF signalling and serotonergic transmission has been unveiled: serotonin (5-HT) stimulates the expression of BDNF, while BDNF in turn enhances the growth and survival of 5-HT neurons [60]. Furthermore, childhood maltreatment elevates the risk of persistent depression if individuals carry two short alleles of the serotonin transporter gene linked promoter region polymorphism (5-HTTLPR) [61]. These findings support an interaction between environmental, developmental and genetic factors on the risk to develop depression.

The mentioned 5-HTTLPR polymorphism also influences how positive and negative emotions are experienced in MDD. Lower efficacy in serotonin re-uptake as a consequence of 5-HTTLPR homozygosity for the short allele (5-HTTLPR SS), correlates with negative emotions, whereas homozygosity for the long allele is associated with positive emotions [62]. Moreover, DNA methylation may be influenced by prolonged stress, thus providing the path for enduring epigenetic changes in behavior [63]. These changes may occur early in life, and the interaction between stress and 5-HTTLPR or other polymorphisms provide the background to the emergence of depression [30, 63]. When under stress, women who are SS carriers are 8 times more prone to develop depression, followed by SS carrier men (4 times), and women carrying at least one L allele (3 times) [64]. The least prone to develop depression when under stress are male L-allele carriers [65]. The cumulative factors of risk for depression are also dependent on the BDNF Val66Met polymorphism [66].

McKinney & Sibelle [33] proposed that LLD is a subtype of depression suggesting a mostly biological basis, with a dysfunction of multiple biological processes. The authors called their model "age-by-disease interaction hypothesis" and suggested that the output of normal biologic processes, such as gene expression in the brain during aging, is forced in LLD due to additional genetic, environmental, and biochemical factors. In other words, they recommended that age-related biological changes of the brain, along with additional factors, can lead to LLD [33].

3. THERAPEUTIC TARGETS OF LATE-LIFE DEPRESSION

Therapeutic targets of late-life depression include pharmacological management, psychological therapy, biophysical therapy as well as exercise as additional treatment option for this group of patients. In the following subchapters, we summarize current approaches and evidences for patients suffering from late-life depression. We focus on the specific aims for that patient group, which may result from comorbid problems, including somatic comorbidities, problems with motion and memory and the use of additional various non-psychiatric medications. Table **1** summarizes the therapeutic targets of late-life depression.

3.1. Pharmacological Strategies in Therapy Refractory Late-life Depression

In this section, we will report results of pharmacological escalation trials in older depressed adults not adequately

Table 1. List of findings regarding therapeutic targets for late-life depression patients.

Therapeutic Option	Findings
Pharmacological management	-More than 80% either inadequate therapy response or early relapse within first 6-12 weeks [69]
	Lithium augmentation: -Full remission in 50% and partial response in another 21% (n = 14) [71] -Positive effects of lithium augmentation (n = 51) [72] -Weak evidence for superior effects of lithium augmentation in non-responders to nortritptyline monotherapy [73]
	Sequential combination, augmentation, and switch of antidepressants: -n = 101 patients initially received nortriptyline for 6 weeks; those not responding received augmentation therapy with lithium for two additional weeks. Non-responders after lithium augmentation: switched to phenelzine with or without lithium augmentation. Final escalation step: ECT or fluoxetine: response to nortriptyline therapy in 72.6%. Of patients receiving lithium augmentation, 35% were responders. Of patients entering and finishing phenelzine treatment, 63.6% responded. 14% of the phenelzine non-responders improved adequately after lithium-augmentation (70). -n= 53: combination with bupropione or nortriptyline, or augmentation with lithium: 60% of patients responded; switch from paroxetine to venlafaxine (n = 12 patients): response rate of 45% [75]. -n= 195: 58% not adequately respond to first line therapy; were set to a combination (with burpopione or nortriptyline) or augmentation (with lithium). Response rates 50% (augmentation due to inadequate initial response) - 66.7% (augmentation due to early relapse) [76]. -n = 40 patients not respond to escitalopram: switching over to duloxetine (average dose of duloxetine: 93 mg/d). 50) full response after 12 weeks [77].
	Augmentation with Aripiprazole: -Response rates of 50% after six weeks in LLD patients [78] -n = 24 patients: 50% remitted after 12 weeks [79].
Psychological therapy	Cognitive & behavioral therapies (CBT): -Large effect sizes for CBT compared with control group; but not superior to other psychological interventions (meta-analysis: (Gould *et al*., 2012; Pinquart *et al*., 2007; Wilson *et al*., 2008). - CBT and PST more effective than other therapies (Cuijpers *et al*., 2014). CBT in combination with an antidepressant: superior than CBT or antidepressant alone.
	Interpersonal therapy (IPT): -In combination with antidepressants: IPT significantly reduce symptoms of depression [82; 83]. -IPT versus CAU: one month after treatment: no significant differences in percentages of responders or remitters between the two groups -No proof that IPT can reduce depressive symptoms in LLD as a stand-alone treatment [84].
	Problem-solving therapy (PST): -Illness-related symptoms significantly reduced through PST (meta-analyses: [86; 87]. -Superior efficacy of PST compared to treatment as usual (TAU) [87](Gellis *et al*., 2008), reminiscience therapy [88], supportive therapy [89], community based psychotherapy [90]. -PST more effective than a number of other forms of psychotherapy (meta-analysis: [80]).
	Reminiscence & life review: -Reminiscence and Life Review effective in treating LLD (meta-analyses: [80; 92; 93]).
Biophysical therapy	Deep brain magnetic stimulation (DBS): -Degree of response differ among studies: six-month rates of success across studies: 41 to 66%. -Sustained amelioration (reduction of 50% in the HAM-D) in 4 out of 6 patients [96; 97]. -Long-term findings: functional improvement and persistence of mood response in 64.3% at the last follow up visit (range 3-6 years) [98]. -Subcallosal tracts: critical stimulating target for antidepressant response elicited by TMS [99]. -Beneficial effect of DBS in the nucleus accumbens (NA) [100] -Sustained improvement (reduction of 50% in the HAM-D) in 45.4% of n=11 subjects [95]. -Initial improvement (at 6 months of treatment) in 40% of patients after stimulation of the ventral capsule/ventral striatum; improvement after a 4 year-follow up: 53.3% [101]. -Improvement in a 49 year patient after activation of inferior thalamic peduncle [102]. -Improvement in another patient after stimulation of habenula [103].

Table 1. contd….

Therapeutic Option	Findings
Biophysical therapy	Vagal nerve stimulation (VNS): -Observation of mood improvement following VNS [107; 108]. -Follow up investigations: beneficial effect of VNS on TRD [109; 110].
	Electroconvulsive therapy (ECT): -Involves the release of multiple neurotransmitters (glumatate, GABA, noradrenalin, dopamine and serotonine) [111; 114]. -Increase of neuronal neurotrophic factors (BDNF, nerve growth factor, GDNF). -No significant increase in the BDNF or GNF levels after ECT treatment [118]. -Stimulation of blood flow in temporal and parietal lobes [115]. -Down-regulation of hypothalamic-pituitary-adrenal (HPA)-axis receptors [111]. - Increased NAA levels in responders [116] -Changes in DTI parameters in the fronto-limbic pathways of depressed subjects [117].
	Repetitive transcranial magnetic stimulation (TMS): -24 week follow-up: high effect (84%) of TMS in the treatment of TDR [126] -Changes in metabolism in the DLPFC through modulation of cerebral excitability and activation of circumscribed areas [120]. -Modulate the metabolism of anterior cingulate cortex (ACC) [121], supplementary motor area (SMA) [122], medial frontal cortex [123] and striatum [124]. -Synaptic transmission influenced by long term treatment of TMS [125].
	Magnetic seizure therapy (MST): -Used to target seizure induction in the prefrontal cortex, reaching also temporal lobe structures, *i.e.*, the hippocampus. -Effects of MST physiologically distinct from ECT, particularly with regards to cognitive impairment [127]; -MST similar effect and feasibility as ECT [128], with greater tolerability [129-131].
Exercise	- evidence that exercise as a potential therapeutic strategy in elderly [132-136]. -Review of RCT-studies (10 studies) with depressive patients > 60 years [135]: exercise / standard treatments / no treatment / placebo-treatment: Majority of studies significant reductions in depressive symptoms after treatment; not all yielded positive results [137-139]: -Blumenthal *et al*. [140]: aerobic exercise program / sertraline / combined treatment (exercise and sertraline): All groups significant reductions on depression scores after treatment, no significant between group effects. -Mather *et al*. [141]: participants not respond to antidepressant medication benefited from exercise. Exercise / health education talks: exercise group better symptom reduction compared to control group. -Singh *et al*. [142]: weight-lifting exercise / educations lectures: Depressive symptoms significantly reduced in intervention group. -McNeil *et al* [143]: exercise / social contact (home visits by a psychology student) / waiting-list control group: Significant reductions in depressions symptoms in both treatment conditions; exercise was significantly superior to waiting-list control group. -Singh *et al*. [144]: high / low-intensity exercise / standard care group: high-intensity group greater symptom reduction than low intensity or control group. -Exercise interventions / educational health groups: no differences in depressive symptomatology [137-139; 145]. -Sjösten & Kivelä [136]: reviewed five studies with inclusion criteria similar to [135]; four yielded positive results [141; 143; 146; 147]. -Exercise associated with improved overall mood [133; 149] and psychological well-being [150]. -Executive control processes, such as planning, scheduling, inhibition, working memory, multi-tasking and dealing with ambiguity benefits from aerobic exercise [153; 154]. -Blake *et al*., review [134]: immediate, medium term (3-12 months) and long term effects (>12 months): Most of studies significant reduction in depressive symptoms, or increased remission from depression. Some studies: insignificant effects for both intervention and control groups. Positive medium-term effects on depression symptoms by half of the studies. Other studies no medium-term effect or varying positive effects according to the type of intervention. those studies who evaluate long-term effects yielded positive outcomes in symptom reduction. -Prospective research: exercise not protect against depressive symptomatology in the future [152]. -Exercise reverse hippocampal atrophy by increasing BDNF [135]. -Exergames (video games that combine game play with exercise) improvement of depressive symptomology, mental health-related quality of life and cognitive performance [155].

Abbreviations: LDD = late-life depression, TRLLD = treatment resistant late-life depression, TRD = therapy refractory depression, ECT = electroconvulsive therapy (ECT), CBT = cognitive & behavioral therapies, PST = problem-solving therapy, IPT = interpersonal therapy, CAU = care-as-usual, TAU = treatment as usual, DBS = Deep brain magnetic stimulation, HAM-D = Hamilton Depression scale, TMS = transcranial magnetic stimulation, VNS = Vagal nerve stimulation, ECT = Electroconvulsive therapy, GDNF = glial cell-derived neurotropic factor, HPA = hypothalamic-pituitary-adrenal, DTI = diffusion tensor imaging, TMS = Repetitive transcranial magnetic stimulation, MST = magnetic seizure therapy. RCT = randomized controlled trials, BDNF = brain-derived neurotrophic factor.

responding to any initial antidepressant therapy. Unfortunately, only little systematic research has been performed so far on treatment strategies in therapy refractory late-life depression (TRLLD). The available research is mostly based on case series, open label trials or retrospective analyses.

Generally (and not restricted to old age depression), national clinical practice guidelines (*e.g*. [67]) recommend to ensure adequate dosing, to check medication compliance and adherence and to perform therapeutic drug monitoring if monotherapy with an antidepressant has not resulted in clinical response after four weeks of treatment. If these measures fail, employment of the following pharmacological strategies is recommended: 1) switching to another antidepressant, 2) augmentation therapy or 3) combination with another antidepressant [19, 67, 68]. Here, we will briefly summarize the outcome of studies investigating pharmacological therapy escalation steps I older patients not adequately responding to initial antidepressive therapy.

In late-life depression, some data suggest that the overall response rates are similar to those in middle-aged and younger adults, but that the time course may be different in some older patients. According to Whyte *et al*. [69], more than 80% of TRLLD patients may show either inadequate therapy response or early relapse within the first 6-12 weeks, with comorbid anxiety symptoms being one of the most important factors associated with slower speed of response [69]. When "young-old" (59-69 years), "middle-old" (70-75 years) and "old-old" (76-99 years) depressed patients were compared, no differences in treatment response speed due to age were found [70].

3.1.1. Lithium Augmentation

In a small study (n = 14) of older depressed individuals [71], lithium augmentation led to full remission in 50% and to partial response in another 21% of cases. Adverse symptoms of lithium therapy were managed in some affected patients by adjusting the dose. These findings are in accordance with positive effects of lithium augmentation found by vanMarwijk *et al*. [72] in older patients (n = 51). However, an open-label trial by Zimmer and collaborators [73] found only weak evidence for superior effects of lithium augmentation in non-responders to nortritptyline monotherapy.

3.1.2. Sequential Combination, Augmentation, and Switch of Antidepressants

In an open-label trial [74], n = 101 patients with MDD (mean age 74 years) initially received nortriptyline for 6 weeks (with therapeutic drug monitoring); those not responding to this therapy received augmentation therapy with lithium for two additional weeks. Non-responders after lithium augmentation got their therapy switched to phenelzine (a MAO-inhibitor), with or without lithium augmentation. The final escalation step consisted of electroconvulsive therapy (ECT) or alternatively, fluoxetine. An efficacy analysis in all patients completing the respective stages of treatment revealed response to nortriptyline therapy in 72.6%. Of the patients receiving lithium augmentation, 35% were responders. Of those patients entering and finishing the phenelzine treatment, 63.6% responded. Only 14% of the phenelzine non-responders improved adequately after lithium-augmentation.

Whyte *et al*. [75] investigated a stepwise combination/ augmentation strategy in n= 53 older depressive patients, failing to respond to a monotherapy with paroxetine: combination with bupropione or nortriptyline, or augmentation with lithium was successively applied in patients failing to respond. Cumulatively, 60% of patients responded to one of the applied combination or augmentation therapies. A switch from paroxetine to venlafaxine (n = 12 patients) revealed a response rate of 45%. Mean time to response was between 6-7 weeks from start of first augmentation or switch of therapy.

In a series of n= 195 older patients (> 70 years) with major depression, 58% did not adequately respond to first line therapy and thus were set to receive a combination (with burpopione or nortriptyline) or augmentation (with lithium). Response rates in those receiving combination or augmentation were between 50% (augmentation due to inadequate initial response) and 66.7% (augmentation due to early relapse) [76].

A total of n = 40 patients with major depression (mean age 74.4 years) who previously did not respond to a therapy with escitalopram, entered an open-label trial, switching over to duloxetine (average dose of duloxetine: 93 mg/d). Fifty percent (50%) of individuals reached full response after a median time of 12 weeks [77].

3.1.3. Augmentation with Aripiprazole

Two open-label trials augmenting an existing antidepressive therapy with aripiprazole were employed: The first one [78] found response rates of 50% after six weeks in older depressed patients (mean age: 63 years), receiving an adjunct treatment with aripiprazole. In the second pilot study [79], n = 24 patients (mean age 74 years) with insufficient response to 16-weeks of treatment with escitalopram, followed by either venlafaxine or duloxetine, received adjunct aripirazol (average dose: 9 mg/d). Of the 24 patients who entered the open-label trial for 12 weeks, 50% remitted.

3.2. Psychological Therapy of Late-life Depression

There is growing evidence for the effectiveness of psychological interventions in late-life depression [80]. However, based on current literature not every psychological intervention proves to be equally effective in treating symptoms of depression in older age groups. Therefore, the focus of this chapter is to discuss the effectiveness of four types of psychological interventions: cognitive & behavioral therapies, interpersonal therapy, problem-solving therapy and reminiscence & life review.

3.2.1. Cognitive and Behavioral Therapies (CBT)

CBT is a widely researched, evidence-based psychological treatment in late-life depression (Evans, 2007; Scogin, Welsh, Hanson, Stump, & Coates, 2005). It is based on the assumption that maladaptive patterns of thought and behavior contribute to the onset and the maintaining of a psychological illness such as depression. To remedy the illness, CBT aims to break the patterns of dysfunctional cognitions and behaviors [24].

Several meta-analyses reported large effect sizes for CBT in comparison to a control group but didn't find that CBT was superior to other established psychological interventions (Gould *et al*., 2012; Pinquart *et al*., 2007; Wilson *et al*., 2008). Only one recent meta-analysis by Cuijpers and colleagues (Cuijpers *et al*., 2014) found that CBT and problem-solving therapy (PST) were more effective than other therapies in treating late-life depression (Cuijpers *et al*., 2014). Furthermore, there is evidence that CBT in combination with an antidepressant (*e.g*. Desipramine) lead to superior results in reducing depressive symptoms than treatment with either CBT or the antidepressant alone.

3.2.2. Interpersonal Therapy (IPT)

IPT asserts that the onset and recurrence of depressive episodes is influenced by relationships between patients and their significant others [81]. It combines techniques known from supportive and psychodynamic therapies. Additionally, IPT includes other strategies such as assessing the symptoms of depression and selecting a focus for the treatment from problem areas such as grief, role transitions, role transitions or interpersonal deficit (Cornes & Frank, 1994).

In combination with antidepressants, IPT has proven to significantly reduce symptoms of depression [82, 83]. However, IPT as a stand-alone treatment has been less thoroughly examined. Indeed, a randomized controlled study conducted by van Schaik and collaborators compared IPT to care-as-usual (CAU) and reported that one month after the treatment no significant differences in percentages of responders or remitters between the two groups were found [84]. Literature thus suggests that while IPT is an efficacious treatment in young and middle-aged patients [85] there is no proof to date that it can reduce depressive symptoms in older age groups as a stand-alone treatment. Therefore, more research is needed to investigate the efficacy of IPT in the treatment of late-life depression.

3.2.3. Problem-Solving Therapy (PST)

PST is a form of psychotherapy that focuses on teaching patients to identify and solve their immediate everyday problems and thereby prevent distress and improves patients' coping skills and prevents distress. The treatment includes teaching the patient to identify problems, come up with a set of possible solutions, decide on one of those, implement the solution and afterwards assess whether the approach was successful [81].

Two meta-analyses examined the efficacy of PST in late-life depression: both reported that illness-related symptoms could be reduced significantly through PST [86, 87]. Moreover, there is evidence of superior efficacy of PST compared to treatment as usual (TAU) [87] (Gellis *et al*., 2008,) reminiscience therapy [88], supportive therapy [89] and community based psychotherapy [90]. Furthermore, these findings are supported by a recent meta-analysis reporting that PST was more effective than a number of other forms of psychotherapy [80].

3.2.4. Reminiscence and Life Review

Reminiscence and life review therapies based on Erikson's last stage of lifespan development entitled "reflection on life" are designed to treat psychological illnesses in people of older age (Erikson, 1959). The term *reminiscence* basically defines the spontaneous recall of memories. *Life review*, however, is considered a systematic process that is usually structured around one or more life themes, such as ones childhood, the experience of being a parent, art in one's life or other topics [91]. In a therapeutic context, reminiscence includes the recall of memories with the goal of focusing on positive life events and thereby enhancing well-being. Consequently, the patient tends to describe events and doesn't judge them on their contribution to the meaning of his life. Life review, on the other hand, usually includes the whole life span of a person and focuses on evaluating events and thereby reframing and integrating them. Thus, the goal of life review is to change one's view of themselves and their life [81]. Either therapy, however, exploits patients' memories to treat late-life depression.

There are many different implementations of Reminiscence and Life Review, rendering comparing efficacies of different intervention techniques a challenging task. Yet, there are three meta-analyses that have found Reminiscence and Life Review interventions to be effective in treating late-life depression [80, 92, 93]. Nevertheless, it was frequently reported that due to the number of different forms of reminiscence and life review therapies, the comparison of the outcomes of different studies was complicated; especially when less structured methods have been applied. Thus, existing results should be considered with caution. More research is needed in this field to be able to compare the efficacy of different therapies.

3.3. Biophysical Treatment Approach of Late-life Depression

3.3.1. Deep Brain Magnetic Stimulation (DBS)

Deep brain stimulation (DBS) was first introduced by [94] and its current application is only possible in clinical studies. The regulation of voltage-dependent neuronal ion channels that lead to high-frequency stimulation of neuronal circuits is one hypothetical mechanism associated with DBS. This regulation may activate distributed forebrain networks modulated by monoamine projections from brainstem nuclei (*i.e.*, dopamine from the ventral tegmental area, serotonin from the raphe nuclei) [95]. Although the use of DBS is associated with successful outcomes in the treatment of TDR on clinical investigations, the degree of response differ among studies: six-month rates of success across studies range from 41 to 66% with sustained and increased response over time. A few studies have shown that the subgenual cingulate region may be hyperactivated in depressed patients [96, 97]. A sustained amelioration, defined by a reduction of 50% in the Hamilton Depression scale (HAM-D), was noticed in 4 out of 6 patients. Long-term findings published by the same researchers reported functional improvement and persistence of mood response in 64.3% at the last follow up visit (range 3-6 years) [98]. A recent evidence by Riva-Posse *et al*. [99] showed that the subcallosal tracts may be a critical stimulating target for antidepressant response elicited by TMS (transcranial magnetic stimulation).

Prior studies conducted by Schlaepfer [100] have also evidenced the beneficial effect of DBS in the nucleus accumbens (NA), corroborated by the higher activation in the NA observed by PET (positron-emissions-tomography). A more recent study, performed by the same group, this time with n = 11 patients, showed a sustained improvement in 45.4% (n=5) subjects. This improvement was considered when there was a reduction of at least 50% in the HAM-D Score [95]. One study of Malone and collaborators (2009) [101] evidenced an initial improvement (at 6 months of treatment) in 40% of patients after stimulation of the ventral capsule/ventral striatum. The improvement after a 4 year-follow up was 53.3% [101]. The activation by DBS in additional areas has been also investigated. One improvement in the recurrent depression was observed in a 49 year patient [102], after activation of inferior thalamic peduncle and, in another patient, after stimulation of habenula [103].

3.3.2. Vagal Nerve Stimulation (VNS)

The vagal nerve stimulation (VNS) was developed in 1985 as an experimental treatment for epilepsy [104]. It is less invasive than DBS. Putative mechanism of VNS is possibly due to the electric stimulation of complex synaptic connections between the vagus and the tractus solitaries, whose projection reach the limbic system and diffuse noradrenergic circuits [105, 106]. The observation of mood improvement following VNS encouraged the use of this technique in patients presenting mood symptoms [107, 108]. Later, follow up investigations evidenced a beneficial effect of VNS on TRD [109, 110].

3.3.3. Electroconvulsive Therapy (ECT)

Electroconvulsive therapy (ECT) has been initially introduced in Italy for the treatment of psychotic symptoms. ECT is associated with rapid onset of action [111] and shows efficacy in 60-70% of cases. There is compelling evidence of ECT efficacy in severe depression [112]. The main indication of ECT in TDR is the presence of suicidal ideation or any threat to life, for instance, refuse to eat or drink or accompanied by delusions [113].

The mechanism of ECT action is not yet fully understood, but presumably involves the release of multiple neurotransmitters [111], such as glumatate, GABA, noradrenalin, dopamine and serotonine [114]. Moreover, the increase of neuronal neurotrophic factors, including the BDNF, nerve growth factor and glial cell-derived neurotropic factor (GDNF). Moreover, the blood flow in the temporal and parietal lobe may be stimulated by ECT [115]. Additionally, a down-regulation of hypothalamic-pituitary-adrenal (HPA)-axis receptors has been reported [111].

Evidence from most structural and functional imaging studies has associated ECT therapy with physiological changes. Merkl and collaborators [116] reported increased NAA levels in responders. Another study found increase of fiber integrity (FA) and decrease of mean diffusivity (MD) and radial diffusivity (RD) throughout ECT treatment in the fronto-limbic pathways of depressed subjects, thereby providing a link between diffusion tensor imaging (DTI) changes and treatment related neuroplasticity [117]. In despite of favoring evidence linking ECT to brain changes, one study did not evidence significant increase in the BDNF and GNF levels after ECT treatment [118].

3.3.4. Repetitive Transcranial Magnetic Stimulation (TMS)

The repetitive transcranial magnetic stimulation (TMS) has been used since 1985 and has been approved in 2008 by the FDA (food and drug administration) for the use in moderate TDR [119]. The mechanism is not entirely known, but it has been associated with metabolism in the DLPFC [120], through the modulation of cerebral excitability and the activation of circumscribed areas. Moreover, the TMS may modulate the metabolism of anterior cingulate cortex (ACC) [121], supplementary motor area (SMA) [122], medial frontal cortex [123] and striatum [124]. Additionally, synaptic transmission may be influenced by long term treatment of TMS (long-term potentiation, LTP) [125]. One 24 week follow-up [126] evidenced a high effect (84%) of TMS in the treatment of TDR. Next studies need to elucidate the distinct effects low and high frequency of TMS as well as its efficacy in the long-term course of TDR.

3.3.5. Magnetic Seizure Therapy (MST)

Magnetic fields have been used to induce therapeutic seizures. The technique was introduced in 2001 (Lisanby *et al*., 2001) and can be used to target seizure induction in the prefrontal cortex, reaching also temporal lobe structures, *i.e.*, the hippocampus.

A few studies advocate that the effects of MST may be physiologically distinct from ECT, particularly with regards to cognitive impairment [127]; additionally MST may offer a similar effect and feasibility as ECT [128], but with greater tolerability [129-131].

3.4. Exercise as Treatment Approach of Late-life Depression

Medical treatment of depression in older patients is complicated because depression remains often unrecognized, elderly are more vulnerable to medication side-effects, polypharmacy and poor adherence to treatment occur. Therefore, complementary treatment strategies are needed to augment the efficacy of treatment on depressed elderly patients [132]. Exercise seems to be a promising approach as there is a growing body of evidence that evaluates exercise as a potential therapeutic strategy in elderly [132-136]. Despite the increasing interest in this research field, the findings on the efficacy of this treatment for depression among the elderly are still inconsistent.

Mura & Carta [135] reviewed randomized controlled trials, comparing exercise to standard treatments, no treatment or placebo-treatment in patients diagnosed with depression and older than 60 years. Ten studies fulfilled these inclusion criteria. Further analysis on the quality of the assessments was conducted. Good methodological quality was defined as the concealment of allocation, if the patients were analyzed in the groups to which they were randomly allocated and if the study was double-blinded. Treatment allocation was adequately conceived in four studies. Intention to treat analysis was performed in five studies and

a double-blinded assessment of the main outcome (reduction in depressive symptoms) was not performed at all. Though not all of these studies yielded positive results [137-139], the majority of the included studies showed significant reductions in depressive symptoms after treatment. To give an overview of study outcomes, studies discussed in the review of Mura & Carta [135] will be illustrated in the following paragraph.

Blumenthal *et al*. [140] investigated the effectiveness of an aerobic exercise program on depression compared to sertraline or combined treatment (exercise and sertraline). All groups exhibited significant reductions on depression scores after treatment, but no significant between group effects were found. Thus exercise was equally effective as sertraline in reducing depression symptoms. Mather *et al*. [141] demonstrated that even those participants who did not respond to antidepressant medication benefited from an anaerobic exercise program. An exercise group (endurance, muscle strengthening and stretching) was compared to a control group, with health education talks. After treatment the exercise group achieved a better symptom reduction compared to the control group. Singh *et al*. [142] compared an intervention group (weight-lifting exercise) to a control group attending educations lectures. Depressive symptoms were significantly reduced at post and follow-up measure in the intervention group. McNeil *et al* [143] compared an exercise to a social contact (home visits by a psychology student) and waiting-list control group. Significant reductions in depressions symptoms occurred in both treatment conditions, but only exercise was significantly superior to the waiting-list control group. Singh *et al*. [144] compared two intervention groups (high versus low-intensity) to a standard care group. The high-intensity group achieved a greater symptom reduction than the low intensity or control group. Comparing exercise interventions to educational health groups, no differences in depressive symptomatology were found [137-139, 145].

Sjösten & Kivelä [136] reviewed studies with inclusion criteria similar to Mura & Carta [135]. Only five studies met their inclusion criteria and four of them yielded positive results [141, 143, 146, 147]. Preliminary results of positive effects of Tai Chi [146, 148] support the need of examining various adjunctive exercise treatments. Analyzing the long-term effects of exercise, the authors concluded that physical exercise might be efficient in the short-term but the effects tend to diminish with time [136]. Beside the reduction of depressive symptomatology, exercise is associated with improved overall mood [133, 149] and psychological well-being in the elderly [150].

Blake *et al*. [134] investigated the immediate, medium term (3-12 months) and long term effects (>12 months) of exercise interventions. Most of the studies exhibited a significant reduction in depressive symptoms, or increased remission from depression immediately after exercise intervention. Some studies identified insignificant effects for both intervention and control groups. Positive medium-term effects on depression symptoms were demonstrated by half of the studies which measured medium-term outcomes. Other studies found no medium-term effect or varying positive effects according to the type of intervention. Most of the studies did not evaluate long-term effects of exercise interventions. Those who did yielded positive outcomes in symptom reduction. Long term effects were found for aerobic exercise but not for resistance training [151]. Findings from prospective research indicate that exercise does not protect against depressive symptomatology in the future [152].

Moreover, exercise has been increasingly evaluated as a potential intervention to enhance brain plasticity and to improve cognitive functioning in older adults. The effect of aerobic exercise on cognition seems to be robust and shows positive effects on both, a wide range of cognitive functions and specific cognitive processes. Especially executive control processes, such as planning, scheduling, inhibition, working memory, multi-tasking and dealing with ambiguity, appear to have the largest benefits from aerobic exercise [153, 154]. Results from animal research support these results since exercise improved performance of animals on hippocampus-dependent tasks [153]. Furthermore, current evidence suggest that exercise appears to block or even to reverse hippocampal atrophy by increasing the brain-derived neurotrophic factor (BDNF) which is associated with neuroplasticity in the elderly [135].

Novel approaches using interactive video games that have a movement or exercise component demonstrate promising results. Rosenberg and her colleagues [155] examined whether *exergames* (video games that combine game play with exercise) are eligible intervention programs for elderly with a subsyndromal depression. They yielded positive results in improvement of depressive symptomology, mental health-related quality of life and cognitive performance.

4. DISCUSSION

The current Review article focuses on therapeutic targets of late-life depression. Based on the assumption that depression is a result of the psychobiological final common pathway, therapeutic targets of late-life depression include pharmacological, psychological, biophysical and exercise treatment approaches. The multifactorial 'final common pathway model' integrates psychodynamic, socio-behavioral, and neurobiologic research into a clinically meaningful framework, and for this reason treatment approaches include multi-modal approaches as mentioned earlier in this paragraph.

One of the most important and commonly used treatment option is the use of *drug therapy* in the elderly depressive patients. As many of the elderly have an individual explanatory model for the depressive symptoms based on biological theories, the compliance taking psychiatric medication in this patient group is quite well. However, to sum up, considering the increasing life-expectancy and prospective increase in geriatric patient numbers, there is currently a paucity of solid research on TRLLD. While open label trials suggest that patients with late life depression may benefit from switched, combined or augmented therapy with antidepressants, the evidence is fairly weak. Controlled, randomized, double-blind trials are warranted in patients with late-life depression in order to generate high quality and

evidence and valid recommendations for pharmacological strategies in therapy refractory geriatric depression.

Various types of *psychological interventions* have proven to be effective in treating late-life depression. Furthermore, there is evidence that a combination of psychotherapy and antidepressant medication shows better results treating depression in older age groups than either treatment on a stand-alone basis. However, psychotherapy is not frequently prescribed to older age groups exhibiting symptoms of depression although older adults tend to be more accepting of a cognitive therapy or a cognitive therapy in combination with antidepressant medication than of a treatment comprising only antidepressant medication (Hanson & Scogin, 2008; Landreville, Landry, Baillargeon, Guérette, & Matteau, 2001). In fact, only 27% of physicians, questioned in a study by Alvidrez and Arean, stated that they would refer an older depressed patient to psychotherapy (Alvidrez & Areán, 2002). Hence, in order to improve health outcomes in older patients dealing with depression, psychotherapy needs to be included in the guidelines for treatment of depression in all age groups. Moreover, treatment strategies normally used in younger depressive patients have to be modified for the target group, in order to make the acceptability better. For instance, *enhancement of activities* – an often used tool for loss of energy and drive in depressive patients – may be improved to consider the physical characteristics of some elderly patients. At the end, there is a need for more and improved psychoeducative tools are necessary to demonstrate the utility of psychotherapy in depression for this target group.

Another treatment tool, providing interesting results even though not commonly used in psychiatric hospital or outpatient therapy is the *biophysical therapy*. There are various options that are TMS (transcranial magnetic stimulation), VNS (vagal nerve stimulation), MST (magnetic seizure therapy), DBS (deep brain stimulation) and ECT (electroconvulsive therapy). Taken together, evidence suggests that biophysical techniques are promising tools for the treatment of TRD. Some of the above-mentioned instruments (*i.e.*, TMS, MST and DMS) showed relative advantage in relation to ECT, particularly on cognitive measurements (attention, retrograde memory, verbal fluency). However, DBS requires neurosurgical procedure and eventual long-term caveats still demand detailed investigation.

To the end, exercise becomes an increasingly used additional treatment option, although also not regularly included in treatment programs for depressive patients (and also for the elderly). The majority of the reviewed studies evaluated exercise treatment as effective in treating depression but these effects do not appear to be stable over longer time periods. Nevertheless, investigations on cognitive functioning support the beneficial effects of exercise treatment in the elderly. Unfortunately, the interpretations of these findings are subjected to some limitations, as a direct comparison between exercise studies is difficult because of high variability of study designs. For instance, the studies varied in sample characteristics (*e.g.* mean age and severity of depression), nature of control comparison group (*e.g.* group attendance versus usual care), type of exercise (*e.g.* aerobic or anaerobic exercise), intensity and duration of exercise, outcome measures used (*e.g.* self-report versus assessment by an observer) and the length of post an follow-up period [134, 156].

LIMITATIONS

The current review is not a systematic review of the literature, but a narrative review about the neurobiological underpinnings and treatment of late-life and treatment resistant late-life depression. Therefore, some important studies may be missing in the text. However, clinical data about late-life and especially treatment-resistant late-life depression is scarce [20]. Morever, the term "therapy resistant" or "treatment refractory" is not used equally across studies and is not well defined. Therapy resistant often is used when depressive patients do not response to pharmacological treatment. As Mulsant and collaborators mentioned [100], unidentified comorbid medical or psychiatric conditions and misdiagnosis may contribute to treatment resistance.

CONCLUSION

In general, for elderly depressive patients, conventional and established treatment options are used. Treatment recommendations favor a multimodal approach, containing psychological and pharmacological treatment and secondary options according to the indication. Evidence indicate that a combination of psychotherapy and antidepressant medication show better results treating depression in older age groups than either treatment on a stand-alone basis. However, mostly accepted by physicians and patients is the pharmacological treatment although evidence suggests that the drug therapy is not that helpful than in younger depressive patients. Biophysical therapy may be useful; nonetheless, further studies employing larger samples and longer follow-up periods, as well as comparatively studies between biophysical techniques, are necessary to establish the validity and reliability of these instruments in the treatment of TRD.

Regarding psychological therapy, cognitive training is the mostly used in elderly patients, caused by accompanying cognitive dysfunction in elderly depressed patients. Moreover, some of the elderly depressive patients suffer from somatic comorbidities coming along with limited motoric flexibility. Normal therapeutic targets for depression, like improve activities, may not be feasible in those cases. However, therapists may train to improve activities that do not include movement (*e.g.* painting or playing games). Exercise as additional treatment has related problems; such as medical concerns to do sports. Though there is an increasing body of evidence that *exercise* reduces depressive symptomatology, improves overall mood, psychological well-being and cognitive functioning in elderly, a direct comparison of the findings is difficult due to programmatic and methodological incoherence. Future research should focus on comparability of study designs and involve novel approaches as *exergames* and adjunctive treatments as Tai Chi since they exhibited promising results and deserve further investigation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

5-HTTLPR	=	promoter region polymorphism
BDNF	=	brain-derived neurotrophic factor
BDNF	=	brain-derived neurotrophic factor
CAU	=	care-as-usual
CBT	=	cognitive and behavioral therapies
CRH	=	cortical releasing hormone
DBS	=	Deep brain magnetic stimulation
DEX	=	dexamethasone test
DTI	=	diffusion tensor imaging
ECT	=	electroconvulsive therapy
FA	=	fiber integrity
GDNF	=	glia cell line-derived neurotrophic factor
HAM-D	=	Hamilton Depression Scale
HPA	=	hypothalamic-pituitary-adrenal
IL	=	interleukin
IPT	=	interpersonal therapy
LDD	=	late-life depression
MD	=	mean diffusivity
MDD	=	Major Depression Disorder
MST	=	Magnetic seizure therapy
NA	=	nucleus accumbens
PET	=	Positron-Emissions-Tomography
PST	=	problem-solving therapy
RCT	=	randomized controlled trials
rTMS	=	repetitive transcranial magnetic stimulation
TAU	=	treatment as usual
TMS	=	transcranial magnetic stimulation
TNF	=	tumor necrosis factor
TRD	=	therapy refractory depression
TRLLD	=	therapy refractory late-life depression
TRLLD	=	treatment resistant late-life depression
VNS	=	vagal nerve stimulation
WM	=	white matter

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