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COGNITION AS A THERAPEUTIC TARGET IN LATE-LIFE DEPRESSION: POTENTIAL FOR NICOTINIC THERAPEUTICS

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Abstract

Depression is associated with impairments to cognition and brain function at any age, but such impairments in the elderly are particularly problematic because of the additional burden of normal cognitive aging and in some cases, structural brain pathology. Individuals with late-life depression exhibit impairments in cognition and brain structural integrity, alongside mood dysfunction. Antidepressant treatment improves symptoms in some but not all patients, and those who benefit may not return to the cognitive and functional level of nondepressed elderly. Thus, for comprehensive treatment of late-life depression, it may be necessary to address both the affective and cognitive deficits. In this review, we propose a model for the treatment of late-life depression in which nicotinic stimulation is used to improve cognitive performance and improve the efficacy of an antidepressant treatment of the syndrome of late-life depression. The cholinergic system is well-established as important to cognition. Although muscarinic stimulation may exacerbate depressive symptoms, nicotinic stimulation may improve cognition and neural functioning without a detriment to mood. While some studies of nicotinic subtype specific receptor agonists have shown promise in improving cognitive performance, less is known regarding how nicotinic receptor stimulation affects cognition in depressed elderly patients. Late-life depression thus represents a new therapeutic target for the development of nicotinic agonist drugs and parallel treatment of cognitive dysfunction along with medical and psychological approaches to treating mood dysfunction may be necessary to ensure full resolution of depressive illness in aging.

Keywords

cognition; depression; late-life; nicotinic acetylcholine receptors; aging

1. Introduction

Cognitive impairment accompanies depression at any age but is an integral feature of late-life depression where impairment may be compounded due to the presence of both the depressive disorder and normal aging processes. Cognitive impairment contributes to morbidity in late-life depression [1] and predicts functional decline [2], poorer response to antidepressants [3–5], and increased risk of recurrence [6]. Late-life depression appears to

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be a syndrome of intertwined cognitive and mood symptoms. The lack of targeted pharmacological treatments for cognitive impairment in late-life depression represents an unmet need and an opportunity for pharmaceutical development.

In nondemented, depressed older individuals, currently available antidepressants produce less than optimal response rates on mood and cognitive symptoms [7]. In individuals whose mood responds to antidepressants, cognitive deficits also improve, but cognitive performance does not reach the level of never-depressed [8–12]. Antidepressant augmentation with drugs may also affect cognition. Open label [13, 14] and placebo-controlled [15] trials showed improved depressive symptoms in elderly patients when the psychostimulant, methylphenidate, was paired with the antidepressant, citalopram, but these studies did not report effects on cognition. A few attempts to use explicit cognitive enhancing agents (e.g. acetylcholinesterase inhibitors) have not had robust results. A small placebo-controlled study found no effect of the glutamatergic NMDA receptor antagonist, memantine, on mood or functional independence [16]. Augmentation of an antidepressant with an acetylcholinesterase inhibitor, donepezil, temporarily improved cognition, but also increased the risk of depression recurrence [17].

Non-pharmaceutical treatments have been investigated in late-life depression but are not widely available. Behavioral therapies targeting depression with executive dysfunction showed modest benefits to mood but cognition was not evaluated [18, 19]. Neuroplasticity-based computer programs have been hypothesized to aid executive dysfunction in late-life depression but results have not yet been reported [20]. Repetitive transcranial magnetic stimulation is a newer technology for alleviating depressive symptoms with brain stimulation, but has not convincingly been found to improve cognitive impairments in depression [21]. Thus, while there is acceptance that treatment of cognition is important to late-life depression [22], a successful treatment is not yet available.

One potential therapeutic target to improve cognitive performance in late-life depression is the cholinergic system. The cholinergic system is the primary neurotransmitter system responsible for cognitive symptoms in normal aging and dementia [23]. Drugs given to healthy volunteers that block cholinergic receptors reproduce cognitive impairments apparent in dementia, particularly in areas of episodic memory, working memory, and attention [24–26]. In dementia patients, antagonist drugs exacerbate the severity of cognitive symptoms [27]. Drugs that stimulate the cholinergic system have the opposite effect, acting as cognitive enhancers. Cholinesterase inhibitors increase extracellular acetylcholine by blocking its break-down and are used to treat individuals with Alzheimer's disease and other dementias [28]. While cognitive impairment in nondemented older adults with depression may not be identical to dementia, cholinergic intervention may be helpful.

Cholinergic stimulation may be important for cognition in late-life depression, but broad, nonspecific increases in cholinergic activation may be detrimental to mood. Cholinesterase inhibitors have a negative effect on mood [17, 29, 30]. Blockade of one of the major cholinergic receptor subtypes, muscarinic receptors, improved mood symptoms [31, 32], suggesting that stimulation of muscarinic receptors could be detrimental to individuals with late-life depression. Since muscarinic antagonism impairs cognition in healthy and depressed groups [24–26, 33], its use in late-life depression would also not be ideal. However, nicotinic receptor stimulation may benefit both cognition and mood, to improve both major symptomatic components in late-life depression.

In this review, we describe the syndrome of late-life depression, as the combination of three overlapping pathologies: depression, cognitive impairment, and brain structural dysfunction. We summarize studies of nicotinic agonists and antagonists to treat mood symptoms of

depression with nicotine and what is known about the cognitive enhancing properties of nicotine in nondepressed individuals. Lastly, as late-life depression is a multi-faceted syndrome without adequate treatment, we propose that combined treatment of an antidepressant to target mood symptoms and nicotinic stimulation to reverse cognitive impairments may produce better remission rates than either treatment alone. Late-life depression should therefore be considered a new target in the field of nicotinic drug development.

2. Phenomenology of late-life depression

2.1. Diagnostic criteria and comorbidity

As reviewed by Alexopoulos (2005) [34], depression is considered ‘late-life’ when occurring in individuals over the age of 60 years. It can be newly expressed in late-life (late-onset) or be lifelong (early-onset). Diagnostic criteria for major depressive disorder in older adults are the same as for younger adults and include depressed mood or diminished interest or pleasure for at least two weeks, severe enough to cause functional impairment. Depressed individuals also exhibit concentration deficits, psychomotor retardation, sleep and appetite changes, fatigue, guilt, and can develop suicidal ideation. Minor depression, characterized by fewer depressive symptoms, is also found in elderly patients. Patients with minor depression can show significant functional disability and roughly one-quarter transition to major depression within two years [35, 36], thus lower intensity of depression can have deleterious consequences in aging as well.

Epidemiologic relationships have been demonstrated to exist between depression and a number of medical illnesses. Depression occurs at high rates in several chronic illnesses: cardiac disease [37–41], diabetes [42], cancer [43, 44], chronic pain [45], and urinary incontinence [46]. Neurologic illness is also associated with increased risk for depression, such as multiple sclerosis, stroke, Parkinson’s disease, and Mild Cognitive Impairment [47, 48]. Chronic illness and associated pain syndromes can increase the risk of developing depression, both in the affected individual and in caregivers [49, 50].

Importantly, the relationship between depression and medical illness is reciprocal. Not only are medical patients and caregivers at high risk for depressive symptoms, individuals who are depressed have poorer medical outcomes. For example, depression is associated with an increased incidence of diabetes [51]. Similarly, compared to nondepressed cardiac patients, the relative risk for cardiac mortality was greater in the presence of minor or major depression [52] and following myocardial infarction, depression predicted increased mortality [39]. In the instance of an acute event, late-life depression compromises recovery. Following a stroke, patients with a Beck Depression Inventory of greater than 10 or meeting the criteria of major depression were more likely to show a poor functional outcome at 15 months post-injury [53]. Not surprisingly, late-life depression increased the risk for activities of daily living disability and mobility disability [54] and was related to increased mortality [55]. The evidence is therefore that depression comorbid with cognitive impairment will worsen medical outcomes. Successful treatment of late-life depression may thus have downstream consequences to improve non-mental health problems.

2.2 Cognitive impairments in late-life depression

Depression at any age is associated with cognitive impairment [56]. Late-life depression may be particularly affected because of the greater severity of cognitive impairment, likely related to the interaction between depression and normal cognitive aging. Figure 1 depicts the greater cognitive impairment seen in late-life depression due to converging effects of depression, aging, and brain structural pathology. While any single insult can lead to

cognitive impairment, with the co-occurrence of two factors, severity of cognitive impairment increases and is greatest in the presence of all three, in late-life depression.

Cognitive impairments accompanying ‘normal’ aging (i.e. without dementia or other psychiatric illness) have been well-characterized [57] and include changes in executive function, episodic memory, working memory, attention, and processing speed. Likely not by coincidence, further cognitive impairment in late-life depression is seen in the same areas [58]. Relative to age- and sex-matched controls, individuals with late-life depression are impaired on tests of memory, executive function, processing and motor speed, planning, nonverbal intelligence, and constructional ability [59–65]. Individuals with late-life depression may be considered to have a double disability relevant to cognition, with greater impairment than young adults with depression or non-depressed elderly.

Highlighting the importance of treating cognitive impairments in late-life depression in conjunction with mood symptoms, the extent of cognitive impairment predicts effectiveness of antidepressants to diminish depression symptoms [22]. Furthermore, more severe cognitive impairments in depressed elderly are associated with more severe depression symptoms [66]; [4, 10] and lower remission rates [4, 5, 67–69]. Geriatric depressed patients who are successfully treated with antidepressants show some improvement in cognitive performance [60, 62, 70–72]. However, cognitive deficits often do not fully resolve with antidepressant treatment [8, 9], even in remitted cases of late-life depression [8–11]. Therefore, separate treatment of cognitive impairment may be necessary to improve outcomes in late-life depression.

The domain of executive dysfunction, involving problems in planning, sequencing, organizing, and abstracting, and its effect on late-life depression outcomes has been a significant focus. A depression-executive function syndrome of late-life has been proposed [5], describing patients with greater executive dysfunction as being more resistant to antidepressant treatment and having poorer long-term outcomes [6, 59, 70, 73] reviewed by [74]. Poor performance on executive functioning tasks predicts lower future remission rates [3, 4] and is associated with poorer acute treatment outcomes [75–78]. Such cognitive deficits tend to be more severe in individuals with late-onset depression compared with early-onset depression [79–81], but impairments were evident for patients with early-onset depression as well [82, 83]. Considering the broad cognitive impairments identified in late-life depression and association between executive impairments with depressive symptoms, cognitive treatment augmentation may need to particularly focus on this domain of functioning.

2.3 Structural brain effects in late-life depression

As with cognitive symptoms, neuroimaging findings in individuals with late-life depression support a combined effect of aging and depression. Brain aging, even in healthy elders, is characterized by subtle cortical atrophy and white matter alterations [84]. These findings are more prominent and severe in depressed elders, who exhibit greater volumetric differences, cortical thinning, and greater white matter deterioration. Late-life depression is associated with widespread volumetric differences in frontal [85–87], temporal [88, 89], and cingulate regions [90]. Volumetric differences are accompanied by significant white matter disease, as measured by diffusion tensor imaging [91–93] and hyperintensities [94, 95]. Hyperintensity lesions (a.k.a. leukoariosis, white matter lesions) are thought to be due to cerebrovascular disease (reviewed by [96]). Late-life depression is associated with greater severity of hyperintense lesions (a.k.a. leukoariosis, white matter lesions) in subcortical gray matter (caudate, thalamus, putamen) [97, 98], subcortical white matter [98–100], and frontal and temporal lobes [85, 101–105] than elderly nondepressed. White matter hyperintensities progress over time in both depressed and nondepressed adults, but depressed adults with a

poor course of depression (i.e. never remitted or relapsed) showed greater change in hyperintensity volume over time [106, 107].

Patients with the most severe volumetric and white matter lesions showed the greatest cognitive impairment on executive functioning tasks [61, 78, 108] and also had the smallest response to antidepressant treatment [92, 109–111]. Similarly, the dorsolateral prefrontal cortex, which is important to executive functioning, had weaker correlated activation with other brain regions when patients were at rest than nondepressed elderly [112]. The impairments of neuronal integrity in late-life depression indicate a multi-faceted disorder affecting numerous brain regions important to both cognition and mood, suggesting an area of overlap in neural mechanism underlying cognitive impairments and mood dysfunction. Potentially, the treatment of cognitive impairment in late-life depression will act permissively to improve the efficacy of antidepressants on mood symptoms.

3. The rationale for cholinergic stimulation in late-life depression

3.1 The cholinergic theory of cognitive aging: Role of the nicotinic system

Cognitive impairments in late-life depression suggest increased expression of age-related cognitive decline, arising from the additional insult of depression. Dysfunction of the cholinergic system has been proposed to underlie cognitive symptoms in dementia and normal aging [113]. In nondemented aging, the basal forebrain cholinergic system does not undergo severe cell loss but is marked with decreased synapses and spines and shorter dendrites (reviewed by [114]). Decreased cholinergic activity in nondepressed elders, compared to young adults, correlates with impaired memory [115]. Challenging the cholinergic system in young adult animals and humans with cholinergic antagonist drugs reproduces cognitive slowing and impairments of older animals and humans [116–120], further implicating decreased cholinergic function in cognitive aging.

The most widely used strategy for stimulating cognition in neurodegenerative disease is by stimulating the cholinergic system with acetylcholinesterase inhibitors [121, 122]. However, the treatment of cognitive impairment in late-life depression, acetylcholinesterase inhibitors are not ideal. The tonic increase in acetylcholine resulting from acetylcholinesterase inhibitors may be an imperfect mechanism for stimulating the cholinergic system, as evidenced by the incomplete restoration of cognition in Alzheimer's disease produced with acetylcholinesterase inhibitor drugs and may imperfectly mimic the phasic glutamatergic-cholinergic interactions necessary for cognitive operations. (reviewed by [123]). In depressed patients, acetylcholinesterase inhibitors are additionally problematic because they may increase depressive symptoms. Increased activity at one class of acetylcholine receptors, muscarinic, has been shown to increase depressive symptoms [32] and conversely blocking muscarinic receptors improves mood symptoms [31]. Targeting treatment to stimulation of the other major class of acetylcholine receptors, nicotinic, may thus benefit cognition without deleteriously affecting mood and may be able to simulate more closely the operation of cholinergic signaling in cognitive operations, e.g. attention.

Studies have examined the effects of normal aging on nicotinic receptor structure and function and found a reduction in nicotinic receptor markers [124]; reviewed by [125]. For example, decreases in nicotine binding have been observed after the fourth decade in the medial temporal [126] and frontal lobes [127], areas important for impaired cognitive processes and show decreased structural integrity in late-life depression. Nicotinic receptors have also been shown to play important roles in the functional impairments of certain neurodegenerative diseases, including Alzheimer's disease [128–130]. The investigation of nicotinic treatment for Alzheimer's disease was originally prompted by the finding of a dramatic decline in nicotinic receptors in Alzheimer's disease [131–133]. Loss of nicotinic

binding sites in Alzheimer's disease patients has been linked to the pathologic hallmarks of plaques and tangles [134], and neuroimaging studies using positron emission tomography demonstrate that the loss of nicotinic receptor binding in Alzheimer's disease is linked to changes in cognitive performance [135, 136]. Since dementia is marked by progressive cognitive impairment across multiple domains, it is likely that loss of nicotinic functioning contributes to cognitive symptoms.

Newhouse and colleagues [24–26] examined how blockade of nicotinic receptors with mecamylamine affected performance on a learning task in younger adults, healthy older adults, and patients with Alzheimer's disease and found that nicotinic blockade impaired cognitive performance in all groups in an age- and disease-dependent way. Thus, blockade of nicotinic receptors with mecamylamine models age- and disease-related impairments in learning.

Little work has examined changes in nicotinic receptors in major depressive disorder. In young adults, single photon emission computed tomography (SPECT) analysis of nicotinic receptors carrying the $\beta 2$ subunit showed lower availability across all brain regions in acutely ill and recovered depressed subjects, compared to age- and gender-matched controls [137]. Nicotinic receptor availability correlated with lifetime number of depressive episodes, trauma score, and anxiety score, suggesting that loss of nicotinic availability contributes to the mood symptoms of major depressive disorder. Studies have not extended into elderly depressed patients, but prior studies in young depressed and non-depressed elderly suggests that age- and disease-related changes in nicotinic functioning contributes to cognitive impairment in late-life depression.

3.2 Effects of nicotinic stimulation on cognition in normal humans

Neuronal nicotinic receptors are found throughout the central nervous system. Stimulation of nicotinic receptors may have broad effects on brain function via stimulation of the release of a variety of transmitters involved in cognitive function, including acetylcholine, dopamine, norepinephrine, serotonin, and glutamate [138, 139]. Cognitive improvement is one of the best-established therapeutic effects of nicotinic stimulation. A recent meta-analysis of over 41 double-blind placebo-controlled laboratory studies by Heishman and colleagues concluded that there are significant positive effects of nicotinic stimulation with nicotine on motor abilities, attention, and memory which likely represent true performance enhancement [140]. The nicotinic system has been proposed to have a specific modulatory role in controlled attentional processing when task conditions are difficult [141–144]. Nicotine improves performance in smokers on attentionally and cognitively demanding vigilance tasks [145–147] in the absence of withdrawal effects [140, 148–150]. In nonsmokers, nicotine speeds reaction times on attention tasks [151]. Potter et al. (2012) found no effect of nicotine on behavioral inhibition in healthy young nonsmokers [152], while improving behavioral inhibition performance in adult attention deficit-hyperactivity disorder (ADHD), suggesting that nicotine may act to optimize attentional mechanisms.

Less exploration of nicotinic stimulation with nicotine has occurred in the cognitive domain of working memory (reviewed by [141, 142]). Experimental animal studies demonstrated improvement in working memory with both acute and chronic nicotine treatment in adults [153]. In human smokers nicotine improved spatial attention but impaired spatial working memory [154]. Nicotine enhanced the ability to inhibit a prepotent response in adult smokers [155] and non-smokers [156, 157]. Little is known about effects of nicotinic stimulation on working memory in older populations. Acute, but not chronic, nicotine enhanced working memory in aged rats [158], but in other studies, chronic nicotine treatment enhanced working memory when given at a low dose [159, 160]. Thus nicotinic

stimulation shows potential for benefiting the very cognitive domains impaired in late-life depression.

3.3 Cognitive effects of nicotinic stimulation in clinical populations: nicotine and receptor subtype specific agonists

Newhouse and colleagues first showed evidence of improved memory with intravenous nicotine injection in Alzheimer's disease subjects [161]. Nicotine administration by subcutaneous injection also improved attention-related tasks in Alzheimer's disease [162, 163]. Nicotine skin patch treatment has been found to significantly improve cognitive function in Alzheimer's disease patients [164, 165], but see [166]. The effects of nicotine on the cognitive symptoms of dementia showed improved attention and lessened errors in Alzheimer's disease patients (see [167] for a review). In a recent study, Newhouse [168] showed that six months of nicotine treatment improved attention and episodic memory in patients with Mild Cognitive Impairment, the precursor condition to Alzheimer's disease. This finding highlights the fact that even in older adults with pathological cognitive aging the nicotinic system is still responsive to stimulation. The results of these studies suggest that nicotinic stimulation may have specific benefits on several cognitive domains related to attentional performance and secondarily memory associated with cognitive aging and/or impairment.

Regarding executive function, Potter and Newhouse showed positive effects of nicotinic stimulation on measures in adolescents and adults with ADHD [167, 169] and stimulation of nicotinic receptors may improve both cognitive deficits and symptoms in this disorder [170–173]. In addition, clinical studies, both treatment trials and acute laboratory studies, found that stimulating nicotinic acetylcholine receptors can improve executive function in ADHD and other disorders [171, 174–182]. For example, in schizophrenia, nicotinic stimulation improves both attentional and executive abilities [183, 184].

Neuronal nicotinic receptors are composed of two types of subunits, α and β , of which nine α ($\alpha 2$ – $\alpha 10$) and three β ($\beta 2$ – $\beta 4$) have been found in vertebrates [185–187]. Nicotinic receptors have been shown to be mechanistically involved in cognitive function, and nicotinic innervation of the hippocampus, amygdala and frontal cortex has been demonstrated to be vital to memory function [188]. The two most prevalent nicotinic receptors in the brain are $\alpha 4\beta 2$ and $\alpha 7$, and both have been found to be important for cognitive function [189]. Recently, the distribution of the $\alpha 4\beta 2$ subunit was characterized in the human cortex and found to be most densely localized in the insular and anterior cingulate cortices [190], areas important to cognitive process in depression, indicating that nicotinic receptor availability may be relevant to cognitive dysfunction in late-life depression.

In animal models, agonist drugs targeting the specific subtypes of the nicotinic receptor, $\alpha 4\beta 2$ or $\alpha 7$, enhance working memory [191, 192], social recognition memory [193], and attention [194]. Conversely, antagonism of nicotinic receptors carrying the $\alpha 4\beta 2$ or $\alpha 7$ subunits impair working memory [195]. In humans, Potter and colleagues showed positive effects on learning and memory in Alzheimer's disease of the novel $\alpha 4\beta 2$ nicotinic agonist ABT-418 [196, 197]. In a clinical trials of an $\alpha 4\beta 2$ nicotinic agonist, Dunbar and colleagues (2011) showed that 16 weeks of TC-1734 (AZD 3480) improved attention, episodic memory and a global impression of cognition in patients with age-associated memory impairment [198]. In non-smoking adults with ADHD, the $\alpha 4\beta 2$ nicotinic agonist AZD1446 improved executive functioning [199].

In summary, nicotinic receptors are widely distributed and appear to be intimately involved with a number of cognitive domains impaired in late-life depression. Human clinical and

nonclinical studies suggest that stimulating nicotinic receptor function is practical and potentially therapeutic, particularly in age-related disorders and those with executive dysfunction. Long-term studies of nicotinic drugs have not succeeded in Alzheimer disease dementia, as yet. However, nicotinic stimulation may be most effective in older adults with less severe cognitive impairment and more intact nicotinic receptor systems. The improved cognitive outcome following nicotine treatment in Mild Cognitive Impairment [168] suggests that stimulation of neuronal nicotinic receptors is a promising strategy to ameliorate cognitive symptoms of late-life depression.

3.4 Neuroimaging effects of nicotinic stimulation

The effects of nicotinic cholinergic modulation on cognitive processing and related brain circuitry have been examined in neuroimaging studies (reviewed by [129, 200]). As a result of normal aging, endogenous cholinergic activity may increasingly engage frontally-mediated attentional processes to resolve uncertainties regarding sensory input and the contents of working memory [201]. This may have the effect of producing increased frontal activation that has been seen when older adults perform at the same level as younger adults during functional magnetic resonance imaging. Some studies have shown that this frontal increase is necessary to maintain performance accuracy [202, 203]. Nicotinic receptor dysfunction and loss may reduce the ability for individuals with late-life depression to increase cortical activation during task performance, resulting in significant performance impairments.

There is a large literature on the effects of the cholinergic agonist nicotine on the functional brain circuitry of younger adults. Much of the research in young adults examined smoking status and the functional circuitry involved in attention and working memory affected by nicotine. During attention and memory tasks in smokers, nicotinic stimulation reduces activation in parietal regions [204] and regions associated with the default mode network and internal thought processes [205]. Also in nonsmokers, nicotinic stimulation reduces parietal activation during an attention task [206]. While performing an N-back working memory task, nicotinic stimulation improved accuracy and speeded performance in nonsmokers [207]. Further, Kumari et al. (2003) [207] found that nicotinic stimulation increased activation in brain regions commonly involved in N-back performance [208], i.e. the superior frontal gyrus, anterior cingulate, and the superior parietal cortex. Thus, the effects of nicotinic stimulation are heterogeneous across brain regions, but appear to decrease off-task processing and increase activation of regions relevant to attention and memory performance.

4. Effects of nicotinic receptor stimulation and blockade on depressed mood

A role for the cholinergic system in mediating mood has been long-considered and, recently, nicotinic blockade has been studied for alleviation of mood symptoms in depression. A role for the cholinergic system in mediating mood, originally, emerged from findings that cholinesterase inhibitors increased depressive symptoms in non-depressed [209–211], depressed [30], and remitted depressed individuals [17]. Janowsky (1972) hypothesized that the cholinergic system acts in balance with the adrenergic system to mediate mood, such that depression results from over-activation of the cholinergic system [29]. Supporting a direct effect of cholinergic over-activity in depression, depressed patients showed increased central concentrations of choline, the precursor of acetylcholine [212, 213], which declined following recovery [212].

Depressed patients are twice as likely to smoke as the general population [214], potentially to self-medicate depressive symptoms with nicotine. Ratings of anxiety and depression were progressively higher with heavier smoking habit compared to never smokers [215], and relapse most often occurs in the presence of negative affect [216]. In a prospective study, teenagers with higher depressive scores were more likely to be smokers nine years later [217]. Nicotinic manipulation has shown mixed effects on mood disorders, likely due to smoking history of subjects and the plasticity of nicotinic receptors following prolonged continuous exposure to nicotine. Improved depressive symptoms following nicotinic blockade with the antagonist drug, mecamylamine, were found in patients with tardive dyskinesia [218], particularly in individuals with comorbid major depression [219]. In one study of refractory major depressive disorder patients, mecamylamine was effective as adjuvant to an antidepressant [220]. In rodent models, mecamylamine and competitive nicotinic antagonist, DH β E, also had antidepressant-like properties [221–223]. On the other hand, treatment with nicotine improved mood in nonsmoking major depressed patients [224–226].

Nicotine-induced benefit to mood has been explained as resulting from desensitization of nicotinic receptors following prolonged exposure, such that continued nicotine exposure decreases activity at nicotinic receptors, effectively acting as an antagonist [227, 228]. *In vitro*, nicotinic partial agonists led to inactivation of the $\alpha 4\beta 2$ subtype of nicotinic receptors when applied in the presence of a full nicotinic agonist or applied for a longer duration [229]. In mouse models, improved depressive-like behaviors following treatment with mecamylamine and cytisine, a nicotinic partial agonist, coincided with decreased molecular markers of cell activation [223], indicating that a nicotinic receptor agonist can result in decreased cell activity and depressive symptoms similarly to a nicotinic receptor antagonist. Varenicline is another nicotinic partial agonist at the $\alpha 4\beta 2$ receptor and full agonist at the $\alpha 7$ receptors [230, 231] and is currently used to aid in smoking cessation. Individual case reports have suggested varenicline increased depressive symptoms in some individuals participating in smoking cessation treatment [232–234]. However, placebo-controlled studies and meta-analyses did not support this and showed that overall varenicline treatment blunted the increase in depressive symptoms associated with smoking cessation [235, 236]. Analyses of case reports of adverse reactions showed mixed effects of varenicline on suicidal behavior, with reports of increased risk [233] and no change in risk [237], compared to other medications for smoking cessation. In rats, chronic nicotine administration elicited antidepressant-like effects [238–241]. Interestingly, antidepressant effects were also seen following more acute treatment of nicotine or subtype selective nicotinic agonists [240, 241], although it is not known whether nicotinic receptors were desensitized following the shorter schedules of administration in these studies.

Multi-center clinical trials of nicotinic blockade as adjunct therapy to an antidepressant however were ineffective in patients with major depressive disorder who did not respond to treatment with the antidepressant alone. The compound tested, TC-5214, is an S-(+)-enantiomer of mecamylamine and non-competitive antagonist of nicotinic receptors. TC-5214 showed success in rodent models of depression on a thorough behavioral battery [242], but Targacept issued a press release in March of 2012 reporting no significant effect in several clinical trials in patients with major depressive disorder as an adjunct to ongoing antidepressant treatment. Despite the mixed findings of nicotinic stimulation or blockade in mood disorders, it is possible that nicotinic stimulation will improve impaired cognition in depression. Particularly in late-life depression, nicotinic adjunct to antidepressant treatment may provide an additional modality to alleviation of depressive syndrome, by treating the cognitive impairment that is a significant concomitant of depression in aging.

5. Potential role of nicotinic receptor stimulation for the treatment of late-life depression

We propose that late-life depression in particular is dually characterized by mood and cognitive symptoms and should ideally, thus, be treated with an antidepressant and cognitive enhancer. Figure 2 describes how nicotinic receptor stimulation could benefit neural mechanisms underlying cognition and, consequent, cognitive performance. As has been previously reviewed [129], nicotinic administration results in altered brain activity during attentional, memory, and cognitive control tasks. Thus, individuals with suboptimal cognitive performance such as in late-life depression are more likely to benefit from drugs targeting nicotinic stimulation [167]. In such individuals, cholinergic-driven performance improvements may be accompanied by increases in activity of brain regions engaged by those tasks and decreases in off-task areas [243]. We thus propose that nicotinic agonists will increase task-related brain activity in frontal regions engaged in top-down attention and cognitive control. Through this mechanism, we hypothesize that nicotinic stimulation will also result in improved executive function [244]. We propose that nicotinic stimulation would also influence the default mode network activity. The default mode network is a set of midline regions more active at rest that exhibit decreased activity during task performance [245]. Greater activity of default mode network regions during tasks is associated with poorer performance on tests of attention [246, 247], executive function [247], and processing speed [248–250]. Nicotinic agonist administration during tasks decreases activity in default mode network regions including the anterior and posterior cingulate and medial frontal gyri, and precuneus, during task performance [205, 251–253] and at rest [253]. Nicotinic stimulation also enhances the expected inverse coupling between the default mode network and the executive control network [253, 254]. This increase in default mode network deactivation during tasks correlates with improved performance on attentional tasks [251, 255]. We hypothesize that drugs targeting nicotinic stimulation will improve performance on tests of attention, memory, processing speed, and executive function in depressed patients. These changes will be mediated by increased activity in the attentional and cognitive control networks and by conversely decreased activity in default mode network regions during cognitive tasks.

In addition to the direct benefit on cognition, we propose that nicotinic stimulation can also have downstream effects on mood, by alleviating cognitive attributes of depression. Depressed individuals show biases towards negative stimuli [256], reactivity to negative stimuli [257], and maladaptive rumination [258]. By increasing activity in the frontal and cognitive control networks, decreasing activity of the default mode network, and improving executive functioning, nicotinic stimulation may decrease negative thought patterns in depression. With the weaker influence of negative thought patterns, depressed patients may gain greater benefit on mood from structured antidepressive psychotherapies or medication therapy. Cognitive improvements resulting from nicotinic stimulation may, thus, improve cognitive *and* mood symptoms of late-life depression.

6. Conclusions and future perspectives

Late-life depression is a multi-faceted syndrome with marked cognitive impairment that appears to play a substantial role in the poorer prognosis and worse outcome of treatment. We propose that treatment of late-life depression may benefit from a cognitive enhancer targeting stimulation of nicotinic acetylcholine receptors, in addition to standard antidepressant medication. Little is known regarding nicotinic stimulation in depression generally and even less is known regarding such stimulation in elderly depressed patients on cognitive or mood outcomes. Studies are needed to understand how nicotine and agonists targeting nicotinic receptor subtypes affect neural activation patterns during rest and when

processing cognitive tasks and emotional stimuli. Furthermore, studies should examine the domains of cognitive and/ or emotional processing that are most sensitive to nicotinic stimulation. Pilot translational and clinical studies are necessary to validate the hypotheses proposed here and examine the potential directly for nicotinic stimulation to improve cognitive function, mood, and functional outcome in late-life depression. Of particular importance, studies are needed to identify novel nicotinic agonists that can be added to antidepressant treatment for the enhancement of cognition, and potentially mood, in late-life depression, thus representing a new target for nicotinic drug development.

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Figure 1.

Venn diagram summarizing the component pathologies in late-life depression leading to significant cognitive impairment: Cognitive symptomatology of late-life depression arises from the compounded effects of the cognitive effects of depression, cognitive aging, and loss of neural integrity due to structural brain pathology. Intensity of gray represents degree of cognitive/functional disability.

Figure 2.

Model for how nicotinic stimulation may improve cognitive and mood symptoms in late-life depression: Stimulation of neuronal nicotinic receptors improves cognition by increasing task-relevant and decreasing off-task neural activation. Frontally-mediated attention and cognitive control networks will increase in activity or efficiency and the ruminative, default mode network will decrease in activation while individuals are on-task. Greater task-oriented processing will lead to improved attention, response inhibition, and processing speed, which will contribute to improved executive functioning. The cognitive components of the mood dysfunction in depression will also receive benefit from nicotinic stimulation, directly resulting from more efficient neural activation patterns and downstream from improved executive functioning. With less severe bias and reactivity to negative stimuli and decreased maladaptive rumination, antidepressant and/or psychotherapeutic treatment will be more effective in relieving mood symptoms of depression.