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New trends in pharmacological control of neuropsychiatric symptoms of dementia

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Abstract

Abnormal neuronal and synaptic plasticity occurs in Alzheimer's disease (AD) and depression. The latter, particularly late-life, has been recognized as fundamental in the identification of at-risk prodromal stages of AD. The lack of disease-modifying drugs and the off-label use of antipsychotics and antidepressants for neuropsychiatric symptoms (NPSs) have caused a season of therapeutic inappropriateness. To date, the wealth of clinical trials investigating drugs, diverse for structure and mechanism of action, has failed to provide a cure for all the spectrums of NPSs. Psychedelics in microdosing afford promotion of neurogenesis and synaptic plasticity and, recently, have been considered a revolution for the management of depression endowed with faster action and an improved side effect profile than antidepressants. In the current scenario, therefore, the rapid-acting antidepressant esketamine could represent the first-in-class for treatment of NPSs, and this deserves to be demonstrated with an open-label clinical trial.

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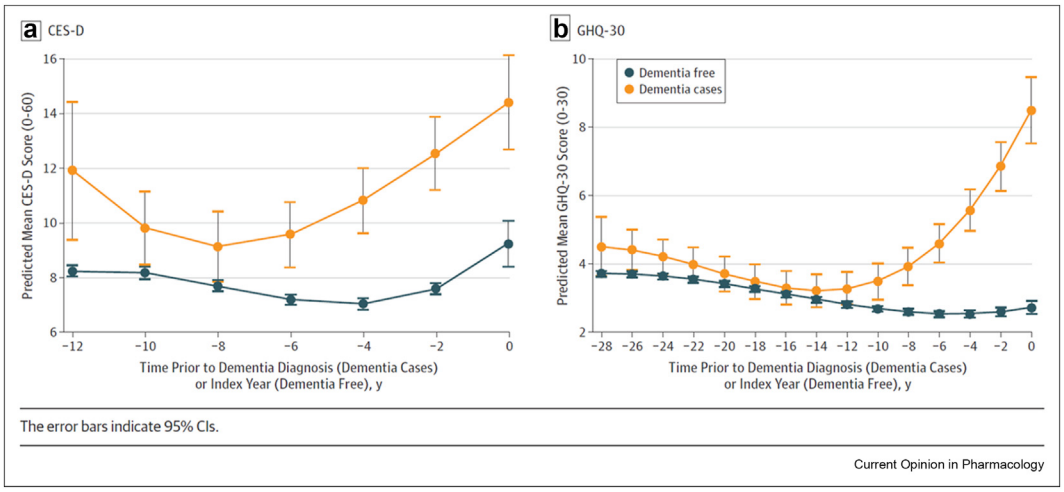
Introduction

Cognitive impairment, characterized by memory pathology with amnestic or nonamnestic-type presentation, has always been identified as the clinical hallmark of Alzheimer's disease (AD). However, during the last years, behavioral disturbances have been gaining growing attention in the landscape of prodromal AD and at-risk stages [1]. AD is a continuum with an insidious onset, and the neuropsychiatric symptoms (NPSs) represent a risk factor for conversion to AD and the earliest red flag of cognitive decline, unfortunately being often under-recognized [2]. The International Society to Advance Alzheimer's Research and Treatment associated with the Alzheimer's Association has described NPSs in the criteria for mild behavioral impairment ([3••, 4]). Mild behavioral impairment is a precursor of after AD and is characterized by decreased motivation and affective dysregulation [4]. Among the NPSs, depression can represent a risk factor, but there is strong evidence for depressive symptoms to be prodromal to the development of dementia with a possible phenomenon of reverse causation (AD neuropathology can induce depressive symptoms years before dementia onset) [5]. During the Whitehall II study, the analysis of retrospective depressive trajectories has demonstrated an accelerated increase in depressive symptoms in the 11 years before dementia diagnosis (difference, 0.61; 95% confidence interval, 0.09−1.13; P = 0.02), increasing more than 9 times at the year of diagnosis ([6••]) (Figure 1).

In particular, late-life depression is associated with cognitive decline ([7••]). In a life-course model, depression is a later-life risk factor for dementia [5] (Figure 2).

The lack of disease-modifying drugs for AD therapy is associated with an inappropriate prescription pattern, and the therapy of NPSs often consists in the off-label use of psychotropic medications ([8−10••]): the latter is devoid of high-quality evidence for efficacy and safety [5]. Clinical trials, meta-analysis, and pool analyses have assessed the efficacy of the symptomatic drugs for AD treatment on NPSs. Current data do not lend support to efficacy of the treatment of depressive symptoms with acetylcholinesterase inhibitors and memantine, but some efficacy of memantine on agitation and on its delay has been demonstrated [11], although its effectiveness on NPSs is still debated [12]. Several drugs with the most disparate mechanisms have been proposed for

Figure 1



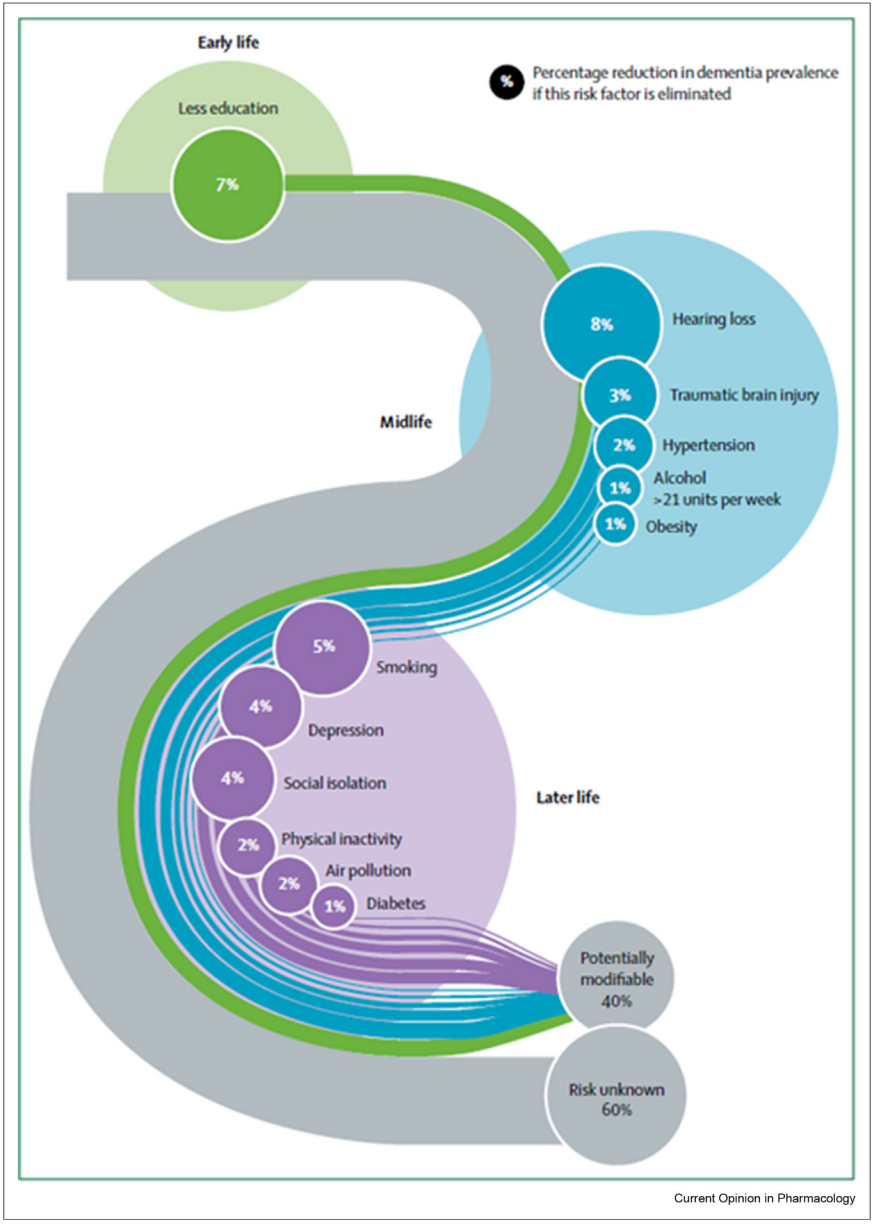
Trajectories of depressive symptoms 12 years (Center for Epidemiologic Studies Depression Scale [CES-D]) before dementia diagnosis and more than 28 years (30-Item General Health Questionnaire [GHQ-30] (reproduced with permission from ([6••])).

repositioning in AD therapy [13]. However, lots of psychotropic drugs have been tested in clinical trials for the management of NPSs without the sound rational basis in support. Therefore, the off-label use of antipsychotics and antidepressants in the control of NPSs is a giant with clay feet. Within this scenario of strong therapeutic inappropriateness, in particular, for the treatment of depression, the aim of this review is to shed light on the most recent advances, also drawing novel paths for the pharmacological treatment of NPSs during dementia.

Depression and Alzheimer's disease

Depression has been hypothesized to represent an enhancer of the progression of dementia in the Delphi consensus [14]. At the following stages of dementia, depressive symptoms are accompanied by agitation, aggressive symptoms, and sleep–wake cycle reversal [14]. In fact, the process of neurodegeneration can enhance the aberrant responsiveness to stressors [5]. This is confirmed at the neuronal level by enhanced vulnerability and altered resilience to stress pathways that increase with aging and in course of neurodegeneration [15]. The altered response to stressors is owing to abnormal neuronal and synaptic plasticity which is common to depression and AD; abnormal neuronal plasticity and synaptogenesis can have a neuroinflammatory and neurotrophic origin [16,17], also converging at the level of glia and overlapping [18]. In fact, there is a vicious cycle between inflammation and the development of neurodegenerative diseases [19]. Aging induces a proinflammatory state in the brain, called inflammaging [19]. Microglia cells operate a regulation of brain inflammation in response to pathogens and danger-associated molecular patterns, but aging causes an impairment of this fine modulation inducing sustained glial activation. Primed microglia produce proinflammatory cytokines, that is, interleukin (IL)-1β, tumor necrosis factor-α, IL-4, IL-6, IL-9, IL-12, and IL-23 [20], and it causes an imbalance between proinflammatory and anti-inflammatory factors. In addition, microglia activation influences the levels of neurotrophins, for example, the brain-derived neurotrophic factor (BDNF) [21]. Age-associated and systemic inflammation-induced morphological changes of microglia are highly dependent on the Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 inflammasome, a multiprotein complex responsible for caspase-1-mediated maturation of IL-1β and IL-18 [22]; in addition, NOD-like receptor family pyrin domain-containing 3 activation is implicated in reduced neurogenesis triggered by neuroinflammatory conditions ([23, 24]). Aging-related depressive symptoms after this brain innate immune system activation are associated with induction of indoleamine 2,3-dioxygenase and to an increased turnover of serotonin (5-hydroxytryptamine, 5-HT) [25]. Furthermore, activated glia can prompt an alteration between synaptic and extrasynaptic glutamatergic neurotransmission [18]. The excitatory amino acid transporters, mainly located perisynaptically on astroglia, regulate the level of glutamate spillover from synapses which is fundamental for the correct neurotransmission [26]. The latter is impaired during neuroinflammation and glial activation [27], causing a derangement of the signaling of N-methyl-D-aspartate (NMDA) and presynaptic metabotropic glutamate receptor 2/3 after reduction of BDNF [28]. This mechanism is confirmed by the action of the glutamatergic modulator ketamine that reduces

Figure 2



Life-course model in dementia prevalence. The life-course model of percentage reduction in dementia prevalence as per the elimination of early-, mid-, and later-life risk factors (reproduced with permission from the study reported by Livingston et al. [5]).

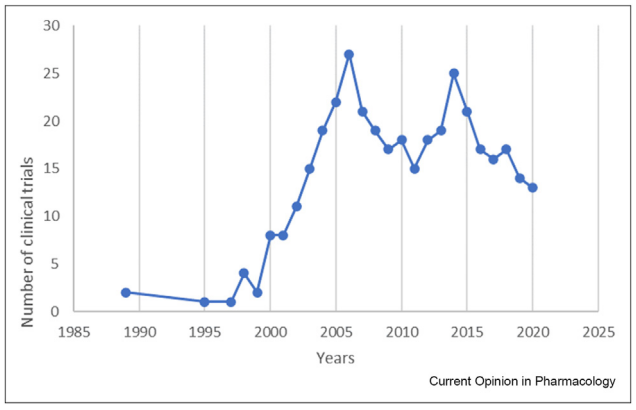
indoleamine 2,3-dioxygenase levels, and it increases kynurenine and kynurenic acid while exerting its fast antidepressant effect [29].

Pharmacological treatment of neuropsychiatric symptoms

In the timeline since the 90s up to the present day, several drugs belonging to the most disparate classes have been tested for the therapy of NPSs. In fact, carrying out a systematic search on PubMed using the query 'pharmacological treatment and NPSs of dementia,' 332 records in the 'clinical trial' field are retrieved (Figure 3). The peak of the studies is in the early 2000s, as demonstrated by most clinical trials assessing the efficacy and the effects on discontinuation of neuroleptics.

In particular, the most studied categories are as follows: typical and atypical antipsychotics (e.g. haloperidol, olanzapine, perphenazine, risperidone); antidepressants (e.g. tricyclic antidepressants, trazodone, and venlafaxine and selective serotonin reuptake inhibitors, i.e. sertraline, and more recently, citalopram and

Figure 3



Number of clinical trials per given years on the pharmacological treatment of the neuropsychiatric symptoms (NPSs) of dementia. Research on the pharmacological treatment of the neuropsychiatric symptoms (NPSs) of dementia. A PubMed search using the keywords 'pharmacological treatment' and 'neuropsychiatric symptoms of dementia' combined through the Boolean operator and has demonstrated an increase of clinical trials from 2 in 1989 to 13 in 2020 (date of last search June 22, 2021) with the first peak on 2006 (27) and the second peak on 2014 (25).

escitalopram); anticonvulsants and mood stabilizers (i.e. carbamazepine, gabapentin, valproic acid); benzodiazepine, for example, lorazepam. The drugs currently used for the management of NPSs are reported in Table 1.

The weakness of the rationale underlying the use of these drugs for the management of NPSs is underscored by the findings: antipsychotics and citalopram at high doses have been effective in some trials, but the overall quality of evidence does not allow a recommendation owing to inconsistency in the single study and among all the studies and small sample sizes [30]. In the above-described frame of uncertainty in the treatment of NPSs, the only drug approved in Europe since 2008 is the atypical antipsychotic risperidone for short-term treatment up to six weeks of severe aggression resistant to nonpharmacological therapy [31]. In fact, often the modest benefit does not overwhelm the toxicity. The antipsychotics are endowed with risk of serious cerebrovascular adverse events, risperidone and olanzapine having been associated to increased risk of cerebrovascular adverse events in a network meta-analysis confirming that none of these drugs is effective and safe overall [32]. The need for novel treatments has also been highlighted by a recent study performed on a cohort of 10106 patients with a diagnosis of dementia demonstrating an increase of antipsychotic-related all-cause mortality risk and, in particular, of hospitalized stroke in patients presenting psychosis but without agitation [33]. Interestingly, when drugs have proven efficacy, this has been on aggression, and in some cases, agitation and psychosis. On the contrary, depressive symptoms have been less studied. In addition, antidepressants are often used for the treatment of agitation and psychosis in these patients, and a Cochrane Database Systematic Review has demonstrated that studies are few and enrolling few participants, underscoring the effectiveness of sertraline and citalopram [34]. Furthermore, a recent Cochrane Database Systematic Review has pointed out the imprecision in the achievement of results of clinical trials assessing the efficacy and safety of antidepressants on depression in course of dementia [35]. The variability in the quality of evidence does not support the efficacy of the latter medications, mainly more than 12 weeks, and no conclusion can be drawn on the whole class and on the single drugs [35].

Advances in the therapy of neuropsychiatric symptoms

The new trends in the study of NPSs have highlighted the importance of serotonergic transmission and of NMDA and metabotropic glutamate receptors that have become the novel target of therapy. The serotonin 5-HT_{2A} receptor inverse agonist and antagonist pimavanserin, approved since 2016 by the Food and Drug Administration (FDA) for the treatment of psychosis in Parkinson's disease, has been studied also in AD. A phase II double-blind, placebo-controlled, single-center, randomized clinical trial (NCT02035553) has demonstrated a significant improvement of psychosis based on the Neuropsychiatric Inventory — Nursing Home Version psychosis score at 6 weeks but not by 12 weeks and not for agitation and aggression and for the Neuropsychiatric Inventory — Nursing Home total score [36]. In fact, a $\geq$30% improvement has been found in the 55% of the pimavanserin group, instead of the 37% of the placebo group [36]. A greater improvement has been observed in a subgroup of patients with severe psychosis [37]. Sponsored by ACADIA Pharmaceuticals Inc, a phase III clinical trial on pimavanserin efficacy in the prevention of relapses of psychotic events but recruiting patients with all-cause dementia (NCT03325556) and an open-label trial for safety and tolerability assessment of pimavanserin over 12 (SERENE NCT02992132) and 52 weeks of treatment (NCT03118947, extension study of the parent trial NCT02992132) have been performed. The 5-HT_{1A}/5-HT_{1B} partial agonist and 5-HT_{2C} receptor agonist eltoprazine are under investigation for the treatment of aggressive symptoms during AD [38]. Randomized, double-blind, placebo-controlled trials have studied the selective serotonin reuptake inhibitor citalopram in AD comparing it to perphenazine (in a short-term study) [39] and to risperidone [40]; an improvement in agitation/aggression and psychosis has been observed not superior to risperidone. In the Citalopram for Agitation in Alzheimers Disease Study (CitAD) multicenter, randomized, placebo-controlled,

Table 1

Pharmacological treatment of the neuropsychiatric symptoms (NPSs) of dementia.

Drug	Class	Daily dosing
Donepezil	Acetylcholinesterase inhibitors	5–10 mg
Rivastigmine	Acetylcholinesterase inhibitors	3–12 mg
Galantamine	Acetylcholinesterase inhibitors	8–24 mg
Memantine	Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists	5–20 mg
Risperidone	Atypical antipsychotics	0.25–2 mg
Olanzapine	Atypical antipsychotics	2.5–10 mg
Quetiapine	Atypical antipsychotics	12.5–300 mg
Aripiprazole	Atypical antipsychotics	5–15 mg
Amisulpride	Atypical antipsychotics	25–50 mg
Clozapine	Atypical antipsychotics	12.5–25 mg
Haloperidol	Typical antipsychotics	0.5–5 mg
Sertraline	Selective serotonin reuptake inhibitors (SSRI)	25–100 mg
Mirtazapine	Selective serotonin reuptake inhibitors (SSRI)	15–30 mg
Citalopram	Selective serotonin reuptake inhibitors (SSRI)	10–20 mg
Trazodone	Tetracyclic serotonin antagonist and reuptake inhibitors	50–150 mg
Lorazepam	Benzodiazepines	0.5–2 mg
Carbamazepine	Anticonvulsants/mood stabilizers	Up to 400 mg

double-blind, parallel-group trial (NCT00898807), citalopram has been studied in combination with a standardized practical psychosocial intervention in patients with probable AD and clinically significant agitation: a reduction of agitation [41] with a sedative component [42] has been demonstrated. Moreover, at week 9, citalopram has resulted effective on hallucinations, but placebo has proven to be favored for sleep disturbances [43]. It is important to consider that, in these patients, citalopram (30 mg/day) has been associated with a remarkable increase in QTc interval [44]. The (S)-stereoisomer of citalopram, escitalopram, has been compared with risperidone for the treatment of agitation and of psychotic symptoms demonstrating no differences in effectiveness between the latter drugs [45], and a phase III randomized parallel assignment clinical trial for the efficacy and safety of escitalopram (NCT03108846) is ongoing. The third-generation antipsychotic brexpiprazole is a dopamine D_2 partial agonist, sharing a serotonergic mechanism owing to its action of a 5-HT_{1A} partial agonist and at a 5-HT_{2A}/5-HT_{2B} antagonist, also acting on noradrenaline α1B/α2C receptors approved by the FDA since 2015 as add-on therapy for schizophrenia and major depressive disorder. It has demonstrated improvement in agitation associated with AD (NCT01862640; fixed doses of 2 mg/day and 1 mg/day) [46]. However, in the second 12-week, randomized, double-blind, placebo-controlled trial (NCT01922258; flexible-dose 0.5—2 mg/day) brexpiprazole has not demonstrated statistical superiority over placebo [46]. An observational study (NCT02192554) has been conducted, and a 12-week extension trial (NCT03594123) is ongoing to deepen the assessment of safety and tolerability. Lumateperone is a novel antipsychotic acting as D_2 and a 5-HT_{2A} antagonist with partial agonism at D_2, acting also at the serotonin transporter, that has been studied for the treatment of agitation in a randomized, double-blind, placebo-controlled trial terminated because prespecified interim analysis has indicated futility (NCT02817906). Dextromethorphan, approved by the FDA as antitussive, is a sigma-1 receptor agonist with activity at the serotonin transporter, NMDA, and α_2 receptors: the latter has been tested in agitation/aggression, in combination with quinidine, to improve its pharmacokinetic profile, in a phase II randomized, multicenter, double-blind, placebo-controlled trial (NCT01584440) showing benefit [47], and novel formulations have been developed for investigation.

Future directions: rapid-acting antidepressants

Depressive symptoms representing a kind of warning sign of prodromal AD are almost neglected from the investigation. Another fundamental issue is raised by toxicity of most of the therapeutic options studied. The lack of an effective and safe treatment for the management of NPSs results in a season of strong therapeutic inappropriateness potentially harmful for this fragile population. Within this framework, a novel path must be taken making use of the important knowledge acquired so far concerned with the mechanisms of neuronal and synaptic plasticity during AD. A drug targeting the latter machinery and able to provide acute relief from symptomatology would be the first-in-class for the treatment of NPSs deserving investigation. New advances underscore the potential for psychedelics to induce synaptic

plasticity and long-term potentiation. The latter drugs modulate serotonergic neurotransmission through 5-HT_{2A} full or partial agonism, if administered in microdoses of one 10th-20th of the recreational dose: this allows promotion of neurogenesis and synaptic plasticity without addiction and hallucinogenic effects [48]. In addition, in the NCT03429075 phase II, double-blind, randomized, controlled trial, psilocybin has been demonstrated to be endowed with faster action and an improved side effect profile than antidepressants ([49,50••]). A single administration of the NMDA antagonist ketamine has been proven to exert a fast antidepressant action lasting ∼2 weeks [51], likely through rapid synthesis of BDNF [52] and anti-inflammatory effects (IL-1β, IL-6, and TNF-α and modulation of the kynurenine pathway) [53]. In 2019, the FDA has approved esketamine, the S-enantiomer of ketamine, as a fast-acting intranasal drug for treatment-resistant depression effective from the second day and beyond 1 month in responders, and the effect does not wane with increasing age ([54••]). Therefore, the RAAD esketamine could represent the first-in-class drug for the treatment of NPSs, and it should be investigated in an open-label clinical trial, head-to-head with risperidone, to assess its efficacy and safety on NPSs in patients with AD. The open design would be required to monitor the acute dissociation induced by esketamine and to guard carefully the possible transient blood pressure increase at around 40 min since administration. Therefore, the RAAD action of esketamine is worthy of investigation for its efficacy and safety of NPSs in AD.

Conclusions

The search for a therapy against AD still represents the greatest challenge to face owing to heterogeneity in biological subtypes [55]. The clinical trials performed so far have failed and, while waiting for the development of effective disease-modifying drugs, drugs with the most disparate mechanisms have been tested for the treatment of NPSs. However, also, in this case, it is possible to notice that all the amounts of clinical trials and even the recent research effort have not provided a definite cure for NPSs. In fact, some drugs have proven efficacy on agitation/aggression and/or psychotic symptoms but not on the whole spectrum of NPSs. Novel advances have proven the capability of psychedelics, esketamine, in particular, to act rapidly after single administration as antidepressants, without chronic side effects. The mechanism implicates promotion of neural plasticity. Gene sets highly expressed in brain regions vulnerable to neurodegeneration are involved in the latter process ([56••]). This treatment deserves investigation because it has the potential to provide for the first time fast-onset long-lasting relief from NPSs without the adverse reactions associated with the current chronic treatments.

Conflict of interest statement

Nothing declared.

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