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Resolving a paradox: antidepressants, neuroinflammation, and neurodegeneration

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Abstract

Depression is a known risk factor for dementia. Antidepressants are the most commonly used treatment for this condition, and are effective in at least half to two-thirds of cases. Extensive evidence from *in vitro* and animal models suggests that antidepressants have anti-inflammatory and neuroprotective properties. These effects have been shown to reduce the oxidative damage, amyloid aggregation, and expression of pro-inflammatory genes associated with animal models of neurodegenerative disorders. However, longitudinal research in humans has shown that antidepressants do not protect against dementia, and may even be associated with a risk of cognitive deterioration over time in older adults. The contrast between two sets of findings represents a paradox of significant clinical and public health significance, particularly when treating depression in late life. This review paper attempts to resolve this paradox by critically reviewing the medium- and long-term effects of antidepressants on peripheral immune-inflammatory responses, infection risk, gut microbiota, and neuroendocrine responses to stress, and how these effects may influence the risk of neurodegeneration. Briefly stated, it is possible that the peripheral actions of antidepressant medications may antagonize their beneficial effects against neuroinflammation. The implications of these findings are then explored with a particular focus on the development and testing of multimodal neuroprotective and anti-inflammatory treatments that could reduce the risk of Alzheimer's and related dementias in patients suffering from depression.

Keywords

Antidepressants, neuroinflammation, neurodegeneration, Alzheimer's disease, cytokines, infection, gut-brain axis, hypothalamic-pituitary-adrenal axis

Introduction

The term "dementia" refers to a clinical syndrome characterized by progressive and usually irreversible impairment in memory and other cognitive functions. Neurodegenerative disorders, particularly

Alzheimer's disease (AD), are the leading cause of dementia worldwide. According to data from the Global Burden of Disease studies, there were over 7.5 million new cases and over 50 million existing cases of Alzheimer's and related dementias in the year 2019. The incidence of these conditions has increased by nearly 150% in the last three decades, and it is projected that the total number of people living with Alzheimer's and other dementias will triple by the year 2050 [1, 2]. There is no known treatment that can reverse or arrest the progression of these conditions, and they are associated with high levels of disability and a significant economic burden [3]. Several risk factors are associated with an increased risk of Alzheimer's and related dementias, and some of these are potentially modifiable. In view of the lack of disease-modifying treatments for these disorders, there has been recent interest in trying to prevent them through early identification and modification of these risk factors through lifestyle, pharmacological, or social interventions [4–6].

Depression is one of the risk factors most consistently associated with Alzheimer's and other dementias. Both longitudinal studies and systematic reviews have identified strong associations between the occurrence of major depressive disorder (MDD) and subsequent diagnoses of dementia in general and AD in particular. These associations appear to be stronger when MDD is diagnosed in later life, but have been documented even when depression occurs in early or middle life [7–12]. The severity of symptoms during episodes of MDD and the number of such episodes have also been associated with an elevated risk of Alzheimer's and related dementias [7, 11]. Some authors have suggested that MDD may represent an early or "prodromal" stage of AD [13]. However, this hypothesis cannot account for cases where there was a significant interval of time between the diagnosis of MDD and the onset of dementia [7, 9]. A more likely explanation for this association is that MDD is associated with immune-inflammatory dysregulation [14–16], which leads to neuroinflammation mediated through activation of microglia [17–20]. This, in turn, leads to cerebral small vessel disease [21], decreases in the volume of key brain areas associated with cognition [22], astrocyte dysfunction [23], and a possible increase in the formation of the cerebral amyloid deposits typically seen in AD [22, 24]. This hypothesis is supported by both translational and clinical evidence, and explains how more severe or recurrent forms of MDD can incrementally increase the risk of dementia [25]. The effect of MDD on the risk of dementia appears to be synergistic with that of other established risk factors, such as gender, age, level of physical activity, smoking, and elevated plasma glucose [26].

As MDD is one of the most common mental disorders worldwide [27, 28], and is generally responsive to pharmacological or psychosocial treatments [29, 30], it offers an attractive, potentially modifiable target for the prevention of dementia. An expert review of the existing literature on MDD and dementia concluded that "The role of pharmacological and nonpharmacological antidepressant strategies in preventing dementia onset and progression warrants further examination by future studies." [31]. Antidepressants are the most prescribed treatments for depression worldwide, and are often the only treatment available in low- and middle-income countries where trained personnel are not available to deliver psychosocial interventions [32, 33]. However, the usefulness of antidepressant treatment of MDD as an approach to dementia prevention has not been systematically studied under controlled conditions [34].

Antidepressants typically act on receptors or transporter proteins for the monoamine neurotransmitters serotonin and noradrenaline [35]. The downstream effects of these drugs are complex [36], but it is hypothesized that they relieve depression through changes in the level of brain-derived neurotrophic factor (BDNF) and increased neurogenesis and neural plasticity in the hippocampus. This is known as the "neurotrophic factor hypothesis". A corollary of this hypothesis is that antidepressants are neuroprotective to a certain extent [37]. It has also been suggested that these drugs also act as anti-inflammatory agents, and are able to reduce both peripheral inflammation and neuroinflammation [38]. Treatment of MDD with antidepressants has been associated with significant reductions in the levels of several pro-inflammatory cytokines, including interleukin-6 (IL-6), IL-10, tumor necrosis factor alpha (TNF-α), and C-C motif ligand 2 chemokine (CCL-2) [39, 40]. These cytokines have the capacity to induce microglial proliferation and inflammation [41], leading to accelerated neuronal loss in AD and related

disorders [42]. The neuroprotective and anti-neuroinflammatory effects of antidepressants have been demonstrated in cell culture and animal models [43]. However, longitudinal research examining the association between antidepressant treatment and dementia risk has yielded unexpected results: Several of these studies found that the use of these drugs either had no effect on the subsequent risk of dementia or paradoxically increased it [44]. The aim of this review paper is to examine the paradoxical "disconnect" between the anti-neuroinflammatory and neuroprotective properties of antidepressants in experimental models of dementia, and the apparently inverse effects seen in some human subjects in real-world settings. This problem is critically examined from several perspectives, and its implications for the development of multimodal dementia prevention strategies are explored.

The role of inflammation in the pathogenesis of MDD

Over the past four decades, evidence for a central role of inflammation in the pathophysiology of depressive disorders has accumulated. Symptoms similar to those of MDD can be observed during a systemic inflammatory response, and have been referred to as "sickness behavior" [45]. MDD is more common in patients with chronic inflammatory disorders [46, 47], and the incidence of depression increases with age in parallel with age-related inflammatory activity [48]. MDD is associated with increased peripheral inflammation even in patients without a comorbid medical illness [49]. This may be due to stress-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated levels of corticotrophin-releasing factor and cortisol, glucocorticoid resistance at the tissue level, and an increase in pro-inflammatory cytokines such as IL-6 [50]. Inflammatory mediators such as IL-1, IL-6, and TNF-α reduce the expression of BDNF, leading to reduced neurogenesis and synaptic plasticity [51, 52]. Patients who respond well to antidepressants show a significant reduction in the cytokine TNF-α [53], suggesting that these drugs have peripheral anti-inflammatory properties. Similarly, drugs that reduce peripheral inflammation have been shown to have anti-inflammatory properties [54]. Peripheral inflammation is correlated with neuroinflammation to some extent [55, 56], and there is evidence of neuroinflammation in patients with MDD [57, 58]. For these reasons, some experts have considered MDD an "inflammatory disorder" [59]. It is likely that the inflammatory changes associated with MDD play a significant role in the link between this disorder and Alzheimer's and related dementias [60, 61].

Antidepressants as anti-inflammatory and neuroprotective agents

A naturally arising question in this context is whether existing antidepressants can meaningfully reduce neuroinflammation [38]. Though this possibility has not been systematically evaluated in patients with MDD, several studies have examined the "anti-neuroinflammatory" potential of antidepressant drugs in cell lines or animal models relevant to dementia [62–79]. Studies examining the beneficial effects of these drugs on neuroinflammation in pre-clinical models are described in Table 1.

These results illustrate the fact that antidepressants of all classes exert inhibitory effects on neuroinflammation, and these effects are directly linked to the pathophysiology of neurodegenerative disorders in many cases [63, 65, 68, 69, 73, 78–81]. These central anti-inflammatory effects are mediated through multiple signaling pathways, including pro- and anti-inflammatory cytokines, intracellular and paracrine signaling cascades, and reductions in oxidative stress and pathological protein deposits [62, 64, 71, 73, 75, 77]. The effects of antidepressants on individual molecular targets vary significantly between drug groups, and even between members of the same group. For example, fluoxetine and sertraline have anti-neuroinflammatory and neuroprotective effects in animal models of dementia, while fluvoxamine and citalopram, which are also SSRIs, do not [72, 77]. Similarly, fluoxetine, but not sertraline, had beneficial effects on an animal model of AD [70]. More interestingly, some of these effects are not related to the inhibition of serotonin reuptake, as they were not observed after direct administration of serotonin [70, 77]. The reason for these differences in anti-neuroinflammatory profiles among antidepressants is unknown, but they may relate to the effects of these drugs on molecular targets other than the serotonin transporter. For example, fluoxetine has agonist properties at the type 2B serotonin receptor ($5HT_{2B}$). In a cell culture model, activation of this receptor by fluoxetine led to indirect activation of the epidermal

Table 1. Effects of antidepressants on neuroinflammation in models related to dementia

Drug class	Drug name	Effects
Tricyclic antidepressants (TCAs)	Amitriptyline	Protects rat cortical neurons against atrophy and synaptic damage induced by TNF-α [62]
		Inhibits NF-κB translocation to the nucleus and IL-1β production in transgenic mouse model of MSA; reduces gliosis in the hippocampus and basal ganglia [63]
	Clomipramine	Reduces LPS-stimulated production of NO, IL-1β, and TNF-α in rodent astrocytes and microglia [64]
	Imipramine	Reduces LPS-stimulated production of NO, IL-1β, and TNF-α in rodent astrocytes and microglia [64]
		Inhibits TNF-α and reduces β-amyloid accumulation in a mouse model of AD; protects against memory impairment [65]
		Inhibits TNF-α-induced expression of CXCL1 in rat astrocytes [66]
		Increases TGF-β expression and reduces IFN-γ expression in rat hippocampus [67]
	Protriptyline	Inhibits NF-κB expression in streptozotocin-induced rat model of AD; improves spatial learning and memory [68]
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	Inhibits NF-κB translocation to the nucleus and IL-1β production in transgenic mouse model of MSA; reduces gliosis in hippocampus and basal ganglia [63]
		Increases TGF-β expression and reduces IFN-γ expression in rat hippocampus [67]
		Restores levels of TGF-β and inhibits Aβ-induced oxidative stress in a mouse model of AD; protects against behavioral changes and memory deficits [69]
		Reduces Aβ-induced toxicity in mixed glia-neuron cultures through conversion of latent to mature TGF-β1 [70]
		Inhibits LPS-induced production of TNF-α and promotes phagocytosis and autophagy in mouse microglia [71]
	Sertraline	Inhibits LPS-induced production of TNF-α and increases IL-10 in mouse astrocytes [72]
		Reduces quinolinic acid-induced elevations in IL-1β, IL-6, and TNF-α and inhibits oxidative stress in a rat model of HD; improves motor functioning [73]
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine	Reduces quinolinic acid-induced elevations in IL-1β, IL-6, and TNF-α and inhibits oxidative stress in a rat model of HD; improves motor functioning [73]
Monoamine oxidase inhibitors (MAOIs)	Moclobemide	Reduces LPS-induced expression of IL-1β and TNF-α in rat mixed glial cells [74]
	Phenelzine	Increases TGF-β expression and reduces IFN-γ expression in rat hippocampus [67]
	Tranylcypromine	Reduces LPS-induced expression of IL-1β IL-6, reduces p-STAT3 and NF-κB nuclear translocation, and reduces TLR4/ERK signaling in mouse microglia; downregulates Aβ-induced microglial activation in a mouse model of AD [75]
Others	Tianeptine	Reduces gp120-induced apoptosis and stimulation of caspase-3, suppresses NOS, and inhibits NF-κB transcription in human astroglial cells [76]
		Inhibits expression of plasminogen activator inhibitor-1 (*Serpine-1*) and reduces lipid peroxidation and apoptosis in mouse cortical neurons exposed to oxygen-glucose deprivation [77]
	Trazodone	Reduces microglial NLRP3 inflammasome expression, phosphorylated p38 MAPK and ATF4 levels, and tau levels in a mouse model of tauopathy; improves sleep and memory [81]
	Vortioxetine	Restores levels of TGF-β and inhibits Aβ-induced oxidative stress in a mouse model of AD; protects against behavioral changes and memory deficits [69]
		Reduces caspase-3 expression and α-synuclein deposition in a rotenone-induced rat model of PD; improves motor, cognitive, and behavioral functioning [78]
	Agomelatine	Reduces expression of aging-related proteins, caspase-3, and glutamate-included excitotoxicity; stabilizes endoplasmic reticulum and mitochondrial membranes in a rat model of aging [79]

Aβ: amyloid-beta protein; ATF4: activating transcription factor 4; CXCL1: chemokine ligand 1; ERK: extracellular signal-regulated kinase; gp120: glycoprotein 120; HD: Huntington's disease; IFN-γ: interferon-gamma; MAPK: mitogen-activated protein kinase; LPS: lipopolysaccharide; MSA: multiple systems atrophy; NF-κB: nuclear factor kappa B; NLRP3: Nod-like receptor protein 3; NO: nitric oxide; NOS: NO synthase; PD: Parkinson's disease; p-STAT3: phosphorylated signal transducer and activator of transcription protein 3; TGF-β: transforming growth factor-beta; TLR4: toll-like receptor 4

growth factor (EGF) receptor on astrocytes, leading to anti-inflammatory and neuroprotective effects [80]. Citalopram does not bind significantly to this receptor, which may explain its ineffectiveness in this context [81].

When these drugs were studied in animal models, their beneficial effects on neuroinflammation also appeared to correlate with positive effects on cognition, behavior, and motor functioning. For example, fluoxetine and vortioxetine reversed the behavioral changes and memory impairment caused by Aβ oligomer administration in a mouse model of AD [69], trazodone improved sleep changes and memory in an inflammation-induced mouse model of dementia [82], amitriptyline improved memory and spatial learning in an oxidative stress model of AD [68], imipramine protected against memory deficits in a different mouse model of AD [65], and venlafaxine improved motor functioning in a rat model of HD [73]. In other words, the beneficial effects of these drugs were not confined to changes in the expression of specific inflammatory markers, but involved improvements in behavioral and cognitive performance.

As antidepressants are widely prescribed and generally have a favorable benefit-to-risk ratio in humans, they represent an attractive approach to neuroprotection in human subjects [38, 43]. Some antidepressants, such as tertiary amine TCAs and the SSRI paroxetine, have significant anticholinergic effects which are undesirable when attempting to prevent dementia [83]. However, other antidepressants, such as secondary amine TCAs, the SSRIs fluoxetine and sertraline, and novel antidepressants such as agomelatine, tianeptine, and vortioxetine, have favorable risk-to-benefit ratios [76–78, 84, 85]. These drugs represent attractive strategies for the prevention of Alzheimer's and related dementias through their effects on neuroinflammation, particularly in patients with past or current MDD [38, 43].

Antidepressants and the risk of dementia in prospective studies

Based on the above results, it would be expected that continuous antidepressant treatment could attenuate the risk of Alzheimer's and related dementias in patients with MDD. Moreover, as many antidepressants have beneficial effects against neuroinflammation that are independent of their inhibition of serotonin reuptake, such an attenuation of risk could be expected even in patients receiving them for indications other than MDD [86]. There are some reports which suggest that this may be the case [87, 88]. However, research in humans reveals a much more equivocal picture [87–103]. The results of these studies are summarized in Table 2.

Two meta-analytic reviews of the literature, covering papers published up to 2017, concluded that antidepressant use was associated with a 1.6- to 3.3-fold increase in the risk of subsequent cognitive impairment of dementia. The risk of dementia was slightly greater with TCAs (relative risk 2.13) than with SSRIs (relative risk 1.75), and was higher when antidepressant treatment was initiated before the age of 65 [104, 105].

Studies published after these meta-analyses were undertaken reveal a mixed picture. Some studies suggest that long-term antidepressant therapy can modestly reduce the risk of dementia in patients with MDD, though not to the level seen in persons not suffering from MDD [86, 99, 101]. Others suggest that antidepressants may have a protective effect against dementia in patients with MDD, but may paradoxically increase the risk of dementia in patients with other diagnoses [91, 96]. It should also be noted that some studies have failed to show evidence of either a risk or a benefit associated with antidepressant use as a whole [98, 100], while others have found an increase in dementia risk [93, 95, 97]. In a large sample of German adults aged 60 years and above, it was found that antidepressants were protective against dementia only in patients with moderate or severe MDD [91]. This finding is of particular interest because secondary analyses of antidepressant trials suggest that they may be superior to placebo only in patients with more severe symptoms of MDD [106, 107]. In other words, they may be ineffective both as antidepressants and as neuroprotective agents in mild MDD.

There are also significant differences in the observed risk or benefit depending on the drug being considered. For example, paroxetine and newer antidepressants are associated with an increased risk of dementia [90, 92, 93], while TCAs as a group do not consistently alter the risk of dementia in either

Table 2. Associations between antidepressant use and the risk of dementia or cognitive impairment

Study	Study population	Results
Goveas et al., 2012 [89]	6,998 women aged 65–79 without dementia	Antidepressant use is associated with a 70% increased risk of MCI over 7.5 years; risk similar for TCAs and SSRIs
Brodrick and Mathys, 2016 [88]	605 patients with MDD aged > 65	Antidepressant treatment for > 5 years is associated with a 4-fold decrease in dementia risk
Lee et al., 2016 [90]	5,394 patients with MDD and subsequent dementia; 5,232 patients with MDD without dementia	All classes of antidepressants except TCAs are associated with a 1.5- to 2.5-fold increase in dementia risk
Jacob et al., 2017 [91]	55,950 patients with MDD without dementia aged 60–80	Antidepressant use protective against dementia (hazard ratio 0.8–0.9) only in patients with moderate or severe MDD
Lee et al., 2017 [92]	1,774 patients with migraine and subsequent dementia and 1,774 patients with migraine and no dementia	SSRIs protective against dementia (hazard ratio 0.6); no change in risk with TCAs; increased risk with newer antidepressants (hazard ratio 4.2)
Then et al., 2017 [93]	5,819 patients receiving antidepressants and 23,276 matched controls	All classes of antidepressants are associated with a 2- to 4-fold increase in dementia risk; a greater increase is seen in patients with diagnoses other than MDD
Bartels et al., 2018 [87]	755 currently non-depressed patients with MCI	In MCI patients with a past history of MDD, > 4 years of SSRI treatment delayed progression to AD; no such effect for other antidepressants
Heath et al., 2018 [94]	3,059 adults aged > 65 without dementia	Paroxetine, but not other antidepressants, associated with a significant increase in dementia risk over > 7 years
Heser et al., 2018 [95]	3,239 elderly patients in primary care without dementia	Antidepressant use associated with a 1.5-fold increase in dementia risk over 12 years; effect significant only for certain drugs in subgroup analyses
Brauer et al., 2019 [96]	4,596 users of trazodone and 22,980 users of other antidepressants	Trazodone is associated with a 1.8-fold increase in dementia risk compared to other antidepressants
Kodesh et al., 2019 [97]	71,515 adults aged > 60 without dementia	Antidepressant monotherapy associated with a 3- to 4-fold increase in dementia risk
Kostev et al., 2019 [98]	20,215 patients with MDD aged 70–90	Reduced risk of dementia with fluoxetine, venlafaxine, and duloxetine compared to citalopram over 10 years
Lin et al., 2020 [99]	550,230 patients aged > 50 receiving antidepressants with or without hypnotics and with no history of dementia	Both antidepressant monotherapy and combined antidepressant/ hypnotic therapy are associated with a 2-fold increase in dementia risk; the possible protective effect of antidepressant monotherapy (hazard ratio 0.4) in the subgroup with MDD
Su et al., 2020 [100]	563,918 patients with MDD aged > 60 in the period 1998–2013	No evidence of increased or decreased risk of dementia with antidepressant use
Babulal et al., 2022 [101]	8,168 participants recruited from 37 United States Alzheimer's Disease Centers	Untreated MDD is associated with a 77% risk of AD; MDD treated with antidepressants is associated with a 45% risk of AD over those without MDD
Tournier et al., 2022 [102]	Healthcare claim data on all adults aged > 50 in the period 2006–2017	No evidence of increased or decreased risk of dementia with antidepressant use
Yang et al., 2023 [103]	354,313 participants aged 50–70 from the UK Biobank	MDD is associated with a 51% increase in dementia risk; antidepressant treatment lowered this risk (hazard ratio 0.7)

MCI: mild cognitive impairment

direction [90, 92]. The SSRI fluoxetine and the SNRIs venlafaxine and duloxetine appeared to have better "protective" effects than the SSRI citalopram [98]. In the most fine-grained analysis of these differences, it was found that antidepressants classified as "potentially inappropriate" for use in the elderly, such as imipramine, amitriptyline, fluoxetine, and tranylcypromine, were associated with a long-term increase in dementia risk, while other antidepressants had neither beneficial nor harmful effects [95]. These findings are inconsistent with the results of animal and *in vitro* models, which suggest that TCAs and newer antidepressants are also protective against neuroinflammation and neurodegeneration (Table 1).

In summary, out of seventeen studies directly examining the association between antidepressant use and dementia, only five found unequivocal evidence for a protective effect of antidepressants [87, 88, 91, 101, 103]; the remainder either yielded mixed results, or found evidence of harm. There are certain other results which indirectly suggest that antidepressants may not be beneficial in preventing Alzheimer's and related dementias. For example, antidepressants may trigger rapid eye movement (REM) sleep behavior disorder, which is an early marker of neurodegeneration [108], and antidepressant treatment does not improve either depressive symptoms or cognition in patients with AD [109, 110].

The contrast between these results and the findings of translational research constitutes a paradox with substantial clinical and research implications. If antidepressants are indeed associated with an increased risk of dementia, is it ethical to prescribe them to patients with MDD, particularly in the elderly? On the other hand, if they have genuine protective effects in some subgroups of patients, should they be continued for longer periods of time or even indefinitely [87, 88]? It is possible that some of the observed discrepancies may be due to methodological variations, or the effects of confounding factors [95, 104, 105, 111, 112]. However, it is unlikely that these can account for the preponderance of negative and mixed findings across countries and drug classes [93, 95, 97, 100]. The rest of this paper will examine the possible mechanisms underlying this paradox, and draw out their implications for novel approaches to the prevention of Alzheimer's and related dementias.

Antidepressants and inflammation: beneficial, harmful, or mixed effects?

Antidepressants are often considered, at least implicitly, to have peripheral and central anti-inflammatory effects. This view is based on the results of pre-clinical research and the apparent decreases in pro-inflammatory cytokines following successful pharmacotherapy of MDD [38–40]. However, it is important to note that most of the changes documented in this research occur over a period of days to weeks. For example, a recent meta-analysis concluded that antidepressant treatment was associated with reduced peripheral levels of IL-6, IL-10, TNF-α, and CCL-2, but the mean duration of follow-up was only 7.6 weeks [40]. In real-world settings, antidepressant treatment is often continued for several months or years [113]. There are relatively few studies examining the medium- or long-term effects of antidepressant therapy on immune system functioning. In a study involving patients on either the TCA nortriptyline or the SSRI citalopram, followed up for over 6 months, decreases were noted in seventeen immune-inflammatory markers, including IL-1β, IL-2, IL-4, IL-7, IL-8, IL-9, IL-13, IL-17, TNF-α, CCL-2, eotaxin-1, and the regulated on activation, normal T cell expressed and secreted chemokine (RANTES) [114].

These findings are important on two counts. First, the changes seen in IL-6 and IL-10 in short-term studies may not be sustained with continued antidepressant treatment. Second, while many of these cytokines are traditionally classified as "pro-inflammatory", others, such as IL-4, IL-10, and IL-13, have anti-inflammatory properties [115–117]. By decreasing levels of both pro- and anti-inflammatory molecules, antidepressant treatment may have complex and perhaps even undesirable effects on immune-inflammatory processes. Third, there are several lines of evidence suggesting that some antidepressants have complex pro-inflammatory effects. In a macrophage model, fluoxetine inhibited the inflammatory response evoked by LPS, but fluoxetine given without LPS induced the production of pro-inflammatory cytokines (TNF-α, IL-6) from these cells [118]. In rats, two to three weeks of fluoxetine therapy was associated with an increase in the pro-inflammatory cytokine IL-2, an increase in cytotoxic CD8+ lymphocytes, and a reduction in regulatory CD4+ lymphocytes [119]. A study of lymphocyte profiles in patients receiving SSRIs for one year found that long-term use with these drugs was associated with a significant increase in natural killer (NK) and B cell counts, but no changes in T cell counts [120]. Similarly, treatment with venlafaxine was associated with a decrease in regulatory CD4+ lymphocytes, while CD8+ cell counts were unchanged [121]. Indirect evidence that long-term antidepressant use may lead to immune-inflammatory dysregulation has been found in patients with ulcerative colitis (UC), a form of inflammatory bowel disease. Patients with UC who received continuous treatment with either SSRIs or TCAs had a more severe illness and a greater requirement for corticosteroid therapy, suggestive of higher local and systemic inflammation; this was not observed in patients receiving intermittent SSRI or TCA treatment [122]. It has also been observed that SSRI use is associated with an increased risk of microscopic colitis [123]. Though these results require replication, they suggest that antidepressants may increase rather than decrease peripheral inflammation in some cases. This can have downstream effects on neuroinflammation. For example, IL-4 can switch microglia from a "classically activated" (M1) to an "alternatively activated" (M2) state, leading to reduced neuroinflammation and neuroprotective effects [124, 125]. IL-10 also has an inhibitory effect on M1 microglia [126]. If IL-4 or IL-10 levels are reduced by prolonged antidepressant treatment, this could lead to a shift in M1/M2 polarization, leading to a

preponderance of M1 microglia and increased inflammation and neurodegeneration. The possible pro-inflammatory effects of antidepressants are summarized in Table 3 below.

Table 3. Evidence for possible pro-inflammatory activity of antidepressants

Data source	Mechanism	Drug(s) implicated
In vitro models	Increased production of IL-6 and TNF-α from macrophages [118]	Fluoxetine
Animal models	Increase in IL-2 and in CD8+ cell count over 3 weeks of treatment [119]	Fluoxetine
Human studies	Decrease in IL-4 over 6 months of treatment [114]	Nortriptyline, citalopram
	Decrease in IL-10 over 8 weeks of treatment [40]	Antidepressants in general
	Increase in NK and B cell counts over 1 year [120]	SSRIs
	Decrease in CD4+ cell counts over 8 weeks [121]	Venlafaxine
	Increased requirement for steroid therapy in UC [122]	Antidepressants in general
	Increased risk of microscopic colitis [123]	SSRIs

Antidepressants and infection: immunosuppressive effects?

In a study of over one million Danish adults, infectious diseases—but not autoimmune disorders—were associated with a 1.5-fold increase in dementia risk later in life [127]. Similar findings have been documented in other settings [128, 129], and across various classes of infectious diseases [130]. The anti-inflammatory effects of antidepressants are often cited as desirable in the context of neuropsychiatric disorders associated with inflammation. However, anti-inflammatory effects could theoretically be associated with a certain degree of immune suppression and an elevated risk of infection. This is particularly important because infections have been associated with an increased risk of subsequent dementia. Studies examining the possible effects of antidepressants on the risk of infection are summarized in Table 4.

Table 4. Possible associations between antidepressants and infection risk

Mechanism or outcome	Evidence
Immunosuppression	Reduced leukocyte count [131]
	Reduced CD4+ count [119, 121]
	Reduced immune response in burns patients [132]
	Impaired tumor surveillance [140]
Increased colonization	Increased nasal bacterial colonization [138]
Increased infection risk	Infections in general [133]
	Post-operative infections [134]
	Respiratory infections [136]
	Clostridium difficile infection [135]
Worse outcomes after infection	Increased mortality in hospitalized patients [137]
Antimicrobial resistance	Selection pressure towards antibiotic resistance in *Escherichia coli* [139]

All classes of antidepressants have been associated with a significant decrease in leukocyte counts over a period of one year [131], and TCA use has been associated with significant immunosuppression in patients with burns [132]. There is also clinical evidence that antidepressant use is associated with an increased risk of several kinds of infections. In an analysis of patient data from the UK Biobank, antidepressant use was associated with an increased risk of infections in patients with mild to moderate MDD [133]. Antidepressants have also been associated with increased rates of infection following colorectal cancer surgery [134], *Clostridium difficile* infection [135], and pneumonia in patients with chronic obstructive pulmonary disease [136], though these effects appear to vary across drug groups. Antidepressant use is also associated with increased mortality in patients hospitalized for infection [137], increased nasal bacterial colonization [138], and selection pressure towards antibiotic resistance in *Escherichia coli* [139]. Furthermore, antidepressant therapy appears to be associated with increased

malignant wound infiltration in patients with cancer, suggesting that they interfere with normal immune surveillance of tumor cells [140]. As mentioned in the previous section, antidepressants such as fluoxetine and venlafaxine may reduce CD4+ lymphocyte counts, leading to increased sensitivity to certain bacterial and viral infections [119, 121]. These findings suggest that the beneficial anti-inflammatory effects of antidepressants may be partially or wholly countered by their effects on the risk of infection, leading to contradictory or inconsistent effects on dementia risk.

Antidepressants, the intestinal microbiome, and the risk of dementia

Recent research has highlighted the central role of the gut-brain axis in mental and neurological health. There are several channels of communication—neurotransmitters, hormones, and immune-inflammatory mediators—that link the enteric nervous system (ENS) of the gut to the central nervous system. Bidirectional "cross-talk" between the ENS and the brain can exert significant effects on mood, cognition, and behavior. This has led some experts to refer to the ENS as the "second brain" [141]. These neurochemical processes are influenced and even regulated by the gut microflora. Alterations in the composition of the intestinal microflora can lead to immune-inflammatory dysregulation, causing neuroinflammation and increased Aβ accumulation [142, 143]. MDD is also associated with alterations in the gut microbiome, and the use of probiotics has been suggested as a novel therapeutic approach in this disorder [144, 145]. Though antidepressants remain the primary mode of treatment for MDD, there is evidence from controlled clinical trials that augmentation with probiotic supplements, containing organisms such as *Bifidobacterium* and *Lactobacillus* species, can improve mood, cognition, and anxiety and reduce levels of pro-inflammatory cytokines in patients with this disorder [146–149]. This has led to interest in the use of such supplements as "psychobiotics"—that is, probiotics specifically developed to have beneficial effects on mental health [150]. Psychobiotics do not only improve symptoms of MDD, but have pleomorphic effects including modulation of the HPA axis, reduction in the levels of pro-inflammatory cytokines, and reduction of oxidative stress. In view of these properties, these microbial strains may have neuroprotective and anti-neurodegenerative effects that are beneficial in AD [151, 152].

The relationship between antidepressant treatment and the gut microbiome is complex and is summarized in Table 5. In a fish model, four weeks of exposure to the SSRI fluoxetine was associated with a decrease in gut commensals and an increase in pathogenic, "pro-inflammatory" bacteria [153]. In contrast, the SSRI escitalopram was associated with an increase in gut microbial diversity in a mouse model of depression; however, this change was noted only in the seven mice classified as "responders" and not in nine "non-responders" [154]. Certain baseline components of the gut microbiome appear to be associated with a better response to SSRIs in MDD [155, 156]. On the other hand, the effects of antidepressant treatment on the gut microbiome vary significantly depending on clinical response. Patients responding well to these medications have greater gut microbial diversity after treatment [157], but do not revert completely to the "normal" profile seen in healthy controls [158]. It has also been observed that some antidepressants exert antimicrobial effects, but whether these have a beneficial impact on gut microbial flora composition is unknown [159, 160]. In fact, there is evidence that antidepressants from all classes (TCAs, SSRIs, and MAOIs) have bacteriostatic or bactericidal effects on normal gut commensals [161]. A recent systematic review concluded that antidepressants often either failed to reduce the gut dysbiosis associated with MDD or slightly increased it [162]. When considering specific bacterial species that are considered protective against depression and neurodegeneration, it has been observed that treatment with fluoxetine resulted in a reduction in *Lactobacillus* and *Bacteroides* species in mice, which was associated with weight loss and anxiety in these animals [163], while escitalopram and mirtazapine inhibited the growth of *Lactobacillus* species *in vitro* [164]. If similar effects occur in human subjects, it is possible that prolonged antidepressant treatment may exacerbate gut dysbiosis. This could contribute to ongoing neuroinflammation and cognitive decline, and provide another plausible pathway linking antidepressant use to the risk of dementia.

Table 5. Effects of antidepressants on the gut microbiome

Data source	Mechanism	Drug(s) implicated
In vitro models	Bacteriostatic effect on *Lactobacillus* spp.	Escitalopram, mirtazapine [164]
	Antimicrobial effect on *Bifidobacterium animalis* and *Bacteroides fragilis*	Desipramine, venlafaxine, bupropion, phenelzine, escitalopram [161]
Animal models	Reduction in colony counts of *Lactobacillus* and *Bacteroides* in mice	Fluoxetine [163]
	Reduction in gut commensals and increase in pathogenic organisms in fish	Fluoxetine [153]
Human studies	Inconsistent effects on gut microbiota, with a possible slight increase in gut dysbiosis	Antidepressants in general [162]

Antidepressants, stress, the HPA axis, and dementia

Chronic stress is a significant risk factor for both MDD and dementia. Exposure to chronic stressors can lead to abnormal activation of the HPA axis, leading to neuroendocrine, immune-inflammatory, and epigenetic changes that may accelerate brain aging, impair cognition, and lead to neuronal loss [23, 165, 166]. Exposure to stressors in early or middle life is associated with a significant increase in the risk of dementia in late life [167, 168], and the presence of stress-related disorders earlier in life is associated with an increased risk of AD [169]. For this reason, some experts have conceptualized AD as a "stress-related disorder" [170].

Stress plays a significant role in influencing the onset and course of MDD, with both first episodes and relapses of MDD often preceded by stressful life events [171–174]. Antidepressants are effective treatments for episodes of MDD, but it is not clear to what extent HPA axis dysregulation predicts antidepressant response, or whether treatment with these drugs normalizes HPA axis functioning. Dexamethasone non-suppression, a measure of impaired HPA axis feedback regulation, has been associated with a better response to TCAs [175]. In contrast, baseline measures of HPA axis overactivity were associated with a worse response to fluoxetine [176] and lower baseline adrenocorticotrophic hormone (ACTH) was associated with a more rapid response to venlafaxine [177]. In the long term, persistent dexamethasone non-suppression despite symptomatic improvement with antidepressants has been associated with an increased risk of relapse [178].

The effects of antidepressants on HPA axis functioning are summarized in Table 6. Imipramine has been found to reduce HPA axis responsiveness over a period of 6 weeks; however, the subjects in this study were healthy volunteers without MDD [179]. In a small study of patients with MDD being treated with fluoxetine or imipramine, neither drug had a significant effect in terms of normalizing serum cortisol levels [180]; a similar study of fluoxetine found that this drug reduced cortisol levels only in those whose depressive symptoms improved [181]. In a comparison of fluoxetine with the TCA nortriptyline, both drugs reduced levels of ACTH but not cortisol [182]. A similar head-to-head comparison of fluvoxamine and amitriptyline found that neither drug normalized the changes in circadian cortisol secretion associated with MDD [183]. Another SSRI, escitalopram, appeared to increase the steepness of the cortisol slope across the day in healthy volunteers, but had no effects on the cortisol response to awakening or total daily cortisol levels [184]. When this drug was used in patients with MDD, it caused a transient change in the cortisol response to dexamethasone in the first week of treatment, but this effect was not observed a month later [185]. Escitalopram also failed to normalize changes in the diurnal secretion of cortisol and ACTH in patients with MDD over a period of 8 weeks [186]. Citalopram, the parent drug of escitalopram, caused an increase in early morning cortisol on short-term administration [187]; longer-term treatment with this drug was associated with reduced HPA axis responsiveness [188]. A similar transient and reversible effect on HPA axis functioning was observed for the atypical antidepressant mirtazapine [189], while the SNRI venlafaxine had no effect on salivary cortisol when given to patients with MDD for four weeks [190]. Finally, a study of patients with treatment-resistant depression, treated with SSRIs or SNRIs, found that antidepressant treatment did not alter the cortisol response to prednisolone administration over three to nine weeks [191].

Table 6. Effects of antidepressants on the HPA axis

Drug group	Drug	Properties
Tricyclic antidepressants	Imipramine	Reduced HPA axis responsiveness over 6 weeks [179]
		No change in cortisol levels over 4 weeks [180]
	Nortriptyline	Reduced ACTH and no change in cortisol over 4 weeks [182]
	Amitriptyline	No effects on circadian variations in cortisol over 6 weeks [183]
SSRIs	Fluoxetine	Reduced ACTH and no change in cortisol over 4 weeks [180, 181]
	Citalopram	Transient increase in morning cortisol after 6 days [187]
		Reduced HPA axis responsiveness over 4 weeks [188]
	Escitalopram	Transient stimulation of cortisol response to dexamethasone at 1 week [184, 185]
		No effects on diurnal secretion of ACTH or cortisol over 8 weeks [186]
	Fluvoxamine	No effects on circadian variations in cortisol over 6 weeks [183]
SNRIs	Venlafaxine	No effects on cortisol over 4 weeks [190]
Other antidepressants	Mirtazapine	Transient increase in morning cortisol after 1 week [189]

Three facts emerge from the existing literature. First, antidepressants do not appear to have a consistent or sustained effect on HPA axis functioning when used to treat MDD. Second, some antidepressants may be less effective in patients with baseline evidence of HPA axis dysregulation. Third, overactivity of the HPA axis may predict relapses after seemingly successful antidepressant treatment. Moreover, antidepressant treatment itself cannot alter or remove chronic stressors; these need to be addressed through appropriate psychosocial interventions [192, 193]. Thus, antidepressant therapy may effectively reduce symptoms in MDD without reducing either stress exposure or its deleterious neuroendocrine effects, leading to depressive relapses, and adverse effects on cognition, neuronal integrity, and neural plasticity.

The paradox resolved: Why do antidepressants fail to significantly reduce the risk of Alzheimer's and related dementias?

A review of the above evidence provides several plausible biological mechanisms that explain why antidepressants, despite exhibiting anti-neuroinflammatory and neuroprotective effects *in vitro*, do not consistently protect against Alzheimer's and related dementias in humans. These mechanisms include drug-induced immune dysregulation, a possible increased risk of infection, and the limited capacity of these drugs to reduce the harmful effects of gut dysbiosis or chronic stress. These are summarized in Table 7 below.

Table 7. Possible mechanisms through which antidepressants may increase the risk of AD and related dementias

Mechanism	Description
Immune-inflammatory dysregulation	Drug-induced reduction in levels of anti-inflammatory cytokines (IL-4, IL-10, and IL-13); stimulation of NK and B cell activity; shift in microglial activation towards a neuroinflammatory phenotype
Increased risk of infection	Possible immunosuppressive effect caused by reductions in CRP, IL-6, and TNF-α; reduction in white cell count; reduction in CD4+ count
Gut-brain dysbiosis	Drug-induced reduction in gut commensals and increase in pro-inflammatory bacteria in animal models; antibacterial effect on common gut commensals *in vitro*, including on beneficial species such as *Lactobacillus*
Stress axis dysfunction	Failure to normalize HPA axis dysfunction; reduced effectiveness in the presence of HPA axis dysregulation; persistence of ongoing stressors despite relief of depressive symptoms
Others	Possible acceleration of normal aging in animal models; possible changes in cerebral microvasculature leading to local ischemia; suppression of REM sleep and precipitation of REM sleep behavior disorder

CRP: C-reactive protein

Other explanations are also possible. For example, there is evidence that certain antidepressants may accelerate biological aging, or cause cerebral microvascular changes that may exacerbate a pre-existing neurodegenerative process [194]. Similarly, there is evidence that most antidepressants can reduce REM sleep, and are associated with a two-fold increase in the risk of REM sleep behavior disorder [195, 196].

These changes in the sleep cycle have been found to predict cognitive decline [197]. It is also possible that at least some of the inconsistencies in the existing results (see Table 2) may be due to methodological limitations. For example, none of these studies have examined differences between antidepressant responders and non-responders; it is possible that a protective effect may be seen only in those whose depression responds well to these medications. Likewise, most of this research did not account for other confounding factors that could affect dementia risk, such as diet, physical fitness, genetic risk (e.g., apolipoprotein E gene polymorphisms), comorbid medical illnesses, or exposure to environmental risk factors such as air pollution [198]. Further research in this field should focus on addressing these limitations and confounders in prospective samples.

The evidence reviewed in this paper should not be seen as a cause for pessimism in the use of antidepressants. Depression is one of the leading causes of disability worldwide, and effective pharmacological treatment of MDD has considerable psychological, physical, and social benefits [199, 200]. At the same time, it is necessary to proceed with caution when specifically advocating for the use of antidepressants in the prevention of dementia, and not overstate their benefits for this particular indication [111, 112]. It is equally important to avoid prescribing potentially inappropriate antidepressants to elderly individuals, even if they have intact or only mildly impaired cognitive functions [95]. In addition, understanding the limitations of existing antidepressants vis-à-vis immune-inflammatory, neuroendocrine, and gut-brain axis functioning is key to the development of improved or novel treatments for MDD. Some of these future treatments may prove to be more robustly protective against dementia than existing drugs. For example, ketamine and psilocybin are emerging treatments for depression that do not act through monoaminergic mechanisms. These drugs appear to have beneficial effects on inflammation and gut-brain axis functioning [201–203]. Likewise, psychobiotics may have antidepressant, anti-inflammatory, and neuroprotective effects, and may be useful both in improving treatment outcomes in MDD and in reducing the long-term risk of neurodegeneration [152, 204]. Though these results need to be replicated in human subjects and in clinical settings, it is possible that these drugs may be useful in the prevention of some types of dementia [205, 206].

Most importantly, it would be valuable to design prospective studies in which patients with MDD, treated with different classes of antidepressants, are followed up into late life and assessed for subsequent cognitive impairment or dementia. Such longitudinal studies could analyze the effects of genetic, lifestyle, and environmental factors on the relationship between MDD, antidepressant therapy, and dementia, and could also be used to test the hypothesis that a protective effect if it exists, is confined to patients with moderate to severe MDD and is not seen in mild MDD or other psychiatric disorders. Such research could also incorporate objective measures of cognitive function, inflammation, and neurodegeneration, such as performances on standardized neuropsychological tests, levels of immune-inflammatory markers, and volumes of key brain regions, and assess changes in these parameters over time. This would lead to a better understanding of the risks and benefits associated with antidepressant treatment in middle and late life, and to a more precision-based use of these drugs in patients with MDD, especially when other risk factors for dementia are present.

The results summarized in this review also provide leads towards a multi-modal approach to the prevention of dementia in patients with MDD. Steps towards such an approach are outlined in Table 8. Briefly put, such an approach would include judicious prescription of antidepressants, concurrent psychosocial interventions for the chronic stressors that trigger or perpetuate depression, monitoring for possible adverse effects of antidepressant medication, and lifestyle modification [207–211].

From a research perspective, antidepressants with beneficial effects on neuroinflammation can be used as "lead molecules" to develop anti-neuroinflammatory agents with fewer undesirable adverse effects. For example, TCAs such as amitriptyline could serve as leads for the development of analogues with central anti-inflammatory effects, but without anticholinergic properties. Likewise, the possibility that neuroprotective effects are related to the unique receptor binding profiles of each antidepressant (e.g., $5HT_{2B}$ receptors for fluoxetine) should be investigated *in vitro* or in animal models. More specifically, existing antidepressants should be studied in more detail for their properties beyond monoamine

Table 8. A multimodal approach to the prevention of AD and related dementias in patients with MDD

Principle	Applications
Drug development	Use existing antidepressants with neuroprotective and anti-inflammatory properties in animal or *in vitro* models as "leads" to develop agents that reduce neuroinflammation and have a favorable risk-benefit ratio
Antidepressant therapy	Provide adequate antidepressant therapy for moderate and severe MDD
	Avoid antidepressants with the potential to worsen cognition (e.g., drugs with anticholinergic properties)
	Ensure adequate long-term adherence to treatment
	Monitor cognitive function periodically
	In selected cases, consider novel antidepressant agents (e.g., ketamine, psilocybin)
Reduction of peripheral inflammation	Encourage appropriate lifestyle modifications (e.g., exercise, dietary components with anti-inflammatory or anti-oxidant properties)
	Select antidepressants with documented anti-inflammatory effects
	Consider adjunctive anti-inflammatory agents after appropriate controlled trials
Reduction of infection	Screen for and treat infections in the elderly, even if common or minor (e.g., oral or respiratory infections)
	Monitor white cell counts and consider changing or discontinuing antidepressant therapy if counts are low
Correction of gut dysbiosis	If a patient does not respond to an antidepressant, consider using a drug from a different class or a novel antidepressant
	Adopt lifestyle modifications, particularly with regards to diet
	Consider adjunctive probiotics or "psychobiotics" after appropriate controlled trials
Correction of stress axis dysregulation	Combine antidepressant therapy with psychological interventions to modulate the stress response, enhance coping, and build resilience
	Advocate for social welfare interventions to reduce social isolation and economic hardship in the elderly

transporter blockade: this includes their long-term interactions with the HPA axis [212], intestinal microbiota composition [213], levels of pro- and anti-inflammatory cytokines [214], and the downstream effects of these processes on microglial activation and inflammation in the brain [215]. When investigating these processes, the influence of pharmacogenomic factors should also be taken into account, as it is possible that specific gene variants may influence the effects of antidepressants on neuroprotection or neurodegeneration [216, 217].

Apart from antidepressants, anti-inflammatory drugs with antidepressant properties, such as inhibitors of cyclooxygenase or cytokines, could be investigated for neuroprotective properties, as these molecular pathways have also been implicated in the pathogenesis of AD [218, 219]. This could be done first in suitable *in vitro* models, and later in well-designed clinical trials. It is possible that some of these drugs can be repurposed as neuroprotective agents in elderly individuals with MDD [220, 221]. Similarly, psychobiotics should be investigated both as adjuncts to antidepressant therapy and as potential early interventions for the prevention of dementia [222].

Conclusions

Depression and Alzheimer's and related dementias are closely linked both mechanistically and epidemiologically. Despite their beneficial effects on neuroinflammation *in vitro* and animal models, antidepressants have not been found to consistently reduce the risk of dementia. The explanation for these results may include alterations in immune-inflammatory, gut-brain, and neuroendocrine functioning, as well as a possible increase in the risk of infection. These findings highlight the need for a multifaceted approach to the prevention of dementia in patients with depression. Some of these approaches, such as dietary modifications, exercise, and psychosocial interventions, are already feasible and should be implemented more widely in depressed patients. However, future breakthroughs in this field will require a better characterization of the long-term physiological effects of antidepressants, including their distinctive receptor binding profiles, their effects on HPA axis and gut-brain axis functioning, and their long-term

effects on neuroinflammation. Unravelling these mechanisms may lead to the future development of antidepressants that target multiple molecular pathways (monoaminergic, immune-inflammatory, and neuroendocrine) or the development of rational combination therapies (such as antidepressants combined with anti-inflammatory or probiotic agents). Unique patient factors, such as genetic variations in the molecular targets of antidepressant action, should also be investigated as modifiers of the neuroprotective effects of these drugs. Though it has not been possible to cover the entire body of literature pertinent to this subject, it is hoped that this paper will provide an overview of the key issues at hand and the leads that can be followed in developing more robust neuroprotective therapies in patients with major depression.

Abbreviations

ACTH: adrenocorticotrophic hormone

AD: Alzheimer's disease

Aβ: amyloid-beta protein

CCL-2: C-C motif ligand 2 chemokine

ENS: enteric nervous system

HD: Huntington's disease

HPA: hypothalamic-pituitary-adrenal

IL-6: interleukin-6

LPS: lipopolysaccharide

MDD: major depressive disorder

NK: natural killer

REM: rapid eye movement

SNRIs: serotonin-noradrenaline reuptake inhibitors

SSRIs: selective serotonin reuptake inhibitors

TCAs: tricyclic antidepressants

TNF-α: tumor necrosis factor alpha

UC: ulcerative colitis

Declarations

Author contributions

RPR: Conceptualization, Methodology, Writing—original draft, Writing—review & editing. The author has read and approved the submitted version.

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The author declares that he has no conflicts of interest.

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