Alzheimer's Research & Therapy

REVIEW

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Beyond expectations: investigating nilotinib's potential in attenuating neurodegeneration in Alzheimer's disease

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Abstract

Neurodegenerative diseases, such as Alzheimer's disease (AD), pose a formidable global challenge. While therapeutic options are available, their limitations are significant, necessitating the development of innovative treatment approaches. Here, we highlight the importance of repurposing drugs and discuss the future of drug treatments for AD. We review the potential of tyrosine kinase inhibitors (TKI) for mitigating AD pathology and symptoms, as well as neurodegenerative processes more broadly. We focus on nilotinib, a selective BCR-ABL tyrosine kinase inhibitor, which has unique mechanisms of action involving the modulation of cell responses and removal of toxic proteins associated with AD pathogenesis. Encouraging studies have demonstrated its efficacy, calling for further investigation through clinical trials to assess its potential in various neurodegenerative conditions. However, despite these promising preclinical findings, no clinical studies have yet conclusively demonstrated its efficacy in treating AD. Considering the future directions in AD research, personalized medicine approaches hold promise by incorporating patient-specific factors, including sex and gender differences, to tailor nilotinib treatment for improved efficacy and safety profiles.

Keywords Repurposed, Alzheimer disease, Neurodegeneration, Autophagy, Memory, Protein aggregates

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Introduction

Alzheimer's disease (AD) constitutes the foremost contributor to dementia cases, with symptoms that include cognitive impairment in domains of memory, thinking, and language abilities, as well as the inability to independently carry out activities of daily living [1]. An estimated 6.2 million elderly individuals aged 65 and above are currently living with AD in the United States [2]. It is estimated that 9.3 million individuals in the United States will be affected by AD by the year 2060 [3], highlighting the need for more effective treatment strategies. AD is a complex neurodegenerative disorder characterized by the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) within the brain, consequently leading to neuronal damage (Fig. 1) [4]. The generation of

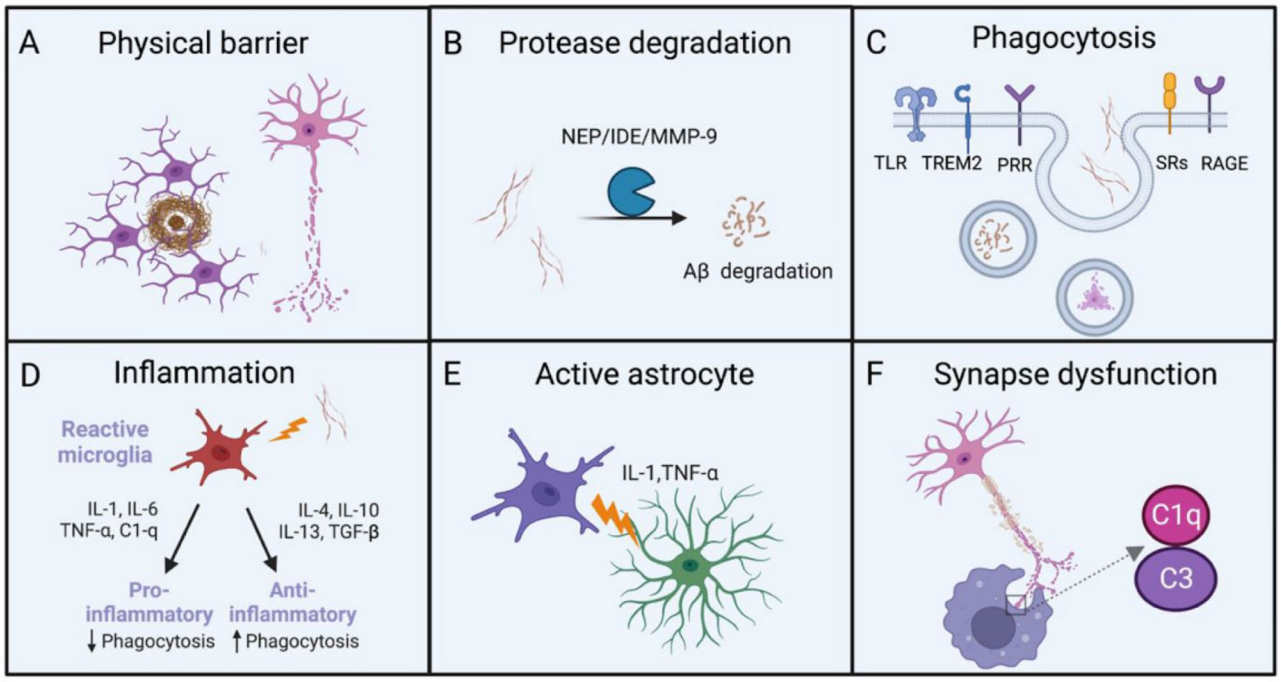

Fig. 1 Schematic depicting glial cell Aβ clearance. AD is characterized by Aβ accumulation, which can cause reactive gliosis in the brain. Nilotinib has been shown to have anti-inflammatory effects and to protect neurons from reactive microglia-induced inflammatory damage. (**A**) To protect neurons from injury by Aβ, microglia form a physical barrier around the Aβ plaque. (**B**) Microglial proteases cause Aβ degradation and increase Aβ clearance. (**C**) Microglial phagocytosis is enhanced by targeting the receptors and pathways involved in this response. (**D**) Anti-inflammatory cytokines promote microglial phagocytosis and Aβ clearance, whereas proinflammatory cytokines inhibit phagocytosis. (**E**) Astrocytes can be activated by cytokines secreted by microglia. (**F**) Aβ can cause microglia to become reactive and impair synaptic function. Reprinted from https://www.mdpi.com/2218-273X/13/2/313. Available under Creative Commons BY 4.0 license

insoluble protein aggregates in the form of Aβ plaques, caused by abnormal cleavage of the amyloid precursor protein (APP), primarily occurs extracellularly [5]. Conversely, hyperphosphorylation of tau protein leads to the collapse of microtubules, resulting in the formation of intracellular NFTs [5]. Due to the complex nature of AD and limited number of effective and safe treatment options approved by the FDA, researchers are actively exploring various molecular mechanisms as potential targets for the development of novel drug therapies. This review aims to explore the potential of repurposing nilotinib, a selective BCR-ABL tyrosine kinase inhibitor originally developed for chronic myeloid leukemia (CML), as a therapy for AD. By examining nilotinib's mechanisms of action, including enhanced autophagy and the reduction of pathological protein aggregates, we evaluate its promise as a disease-modifying treatment for AD.

Current AD treatments

Presently, most FDA-approved drugs for the treatment of AD, including acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists, serve to regulate symptoms rather than modify disease processes [6]. These drugs address the neurotransmitter imbalance associated with AD, employing mechanisms aimed at restoring equilibrium and optimal neuronal functioning [7]. The approved AChEIs for treating AD are donepezil, galantamine, and rivastigmine [8]. AChEIs work (Fig. 2) by enhancing the availability of acetylcholine in the synapse and have demonstrated clinical effectiveness in slowing down cognitive decline in individuals with AD [7].

Another treatment option that has been authorized for moderate to severe AD is memantine, an NMDA receptor antagonist with low-to-moderate affinity, which functions via a noncompetitive mechanism of action [9]. Memantine exhibits the potential to modulate calcium flux that is operated by the NMDA receptor/ion complex. This results in impeding the ion conductance mediated by the NMDA complex and mitigating the troublesome consequences caused by abnormally elevated glutamate levels, which subsequently result in neuronal dysfunction [7, 9, 10].

The newest class of FDA-approved drugs for Alzheimer's disease (AD) target amyloid, with one such drug, lecanemab, being a recently approved monoclonal antibody for patients with mild AD and confirmed Aβ aggregates. Lecanemab has been shown to decrease the burden of Aβ and moderately slow cognitive and functional decline in early-stage cases of the disease [11]. Similarly,

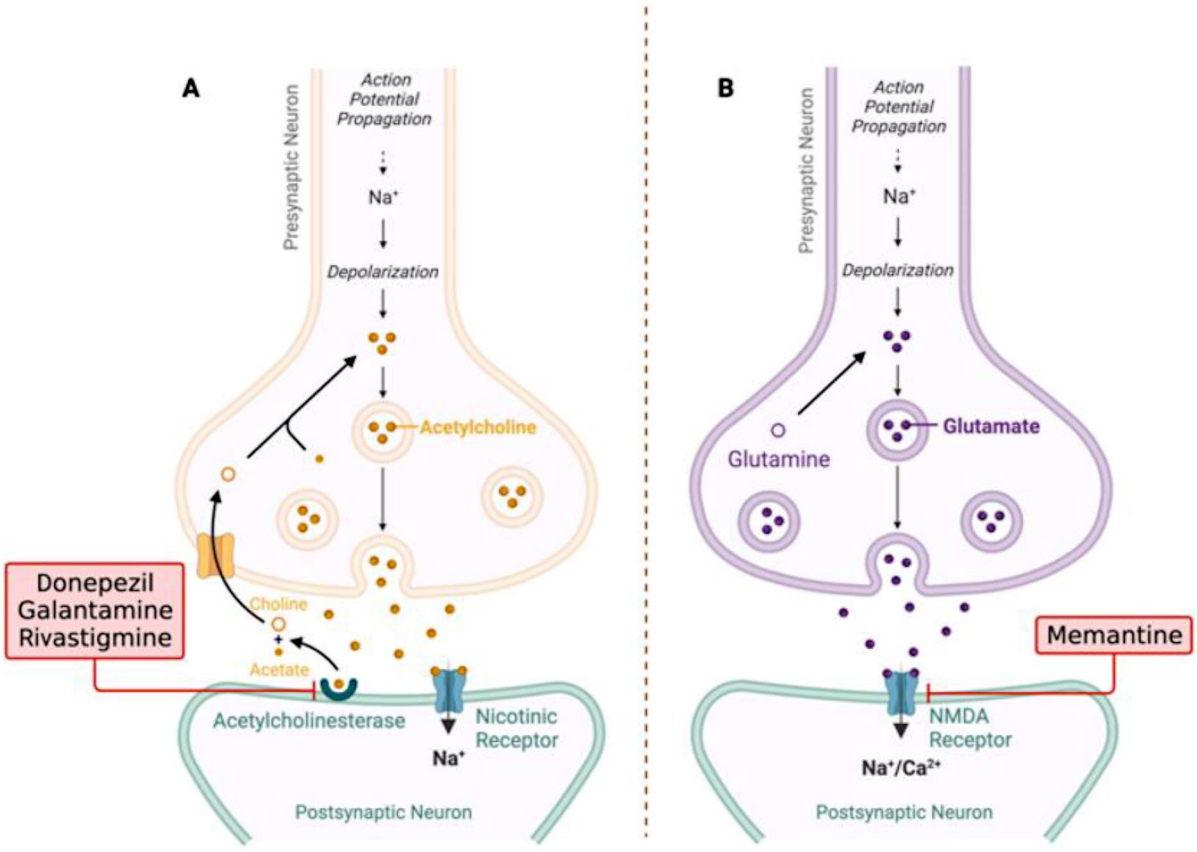

Fig. 2 Reprinted from "Alzheimer's Disease (AD) Treatment Model," by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates/figures. Showing the most common drugs used in the treatment of AD; memantine functioning on the NMDA receptor and donepezil, galantamine, and rivastigmine working on acetylcholinesterase. Not pictured are the newest class of drugs, monoclonal antibodies, that target amyloid to decrease Aβ plaque burden

donanemab, another anti-Aβ monoclonal antibody, binds to the Aβp3-42 subtype targeting Aβ fibrils and has been shown to reduce amyloid levels and detectable tau pathology in the brain as well as potentially slow AD progression in patients with mild AD [12].

Drug repurposing

In the realm of pharmaceutical research, there has been a longstanding practice of employing a *de novo* design strategy to discover drugs [13]. Currently, there has been increasing recognition and acceptance of an alternative approach called "drug repurposing". This approach investigates the potential of existing drugs to treat diseases beyond their originally intended purposes.

One notable advantage of this approach is that the drug already has an existing safety and pharmacokinetic profile. This removes the need for further clinical testing and toxicology studies [14]. Another advantage of this approach is that it allows for circumventing time-consuming early preclinical, phase II, and phase IIa trials, all of which are associated with considerable drug attrition [15]. Various avenues can be explored to identify potential candidates for drug repurposing, and one such methodology involves leveraging expansive datasets to unveil drug-related patient outcomes that may have otherwise remained undiscovered [14, 16]. Another route of investigation lies in hypothesis-driven repurposing [17], where information about the disease of interest and the characteristics and targets of existing drugs for different conditions are integrated to identify potential candidates. Given the current therapeutic strategies and their constrained efficacy, drug repurposing holds significant potential for uncovering novel treatments for AD.

Artificial intelligence and drug repurposing

The impact of artificial intelligence (AI) on drug repurposing is noteworthy in light of its growing prominence. An article of particular interest emphasizes the pivotal role of AI, specifically machine learning, in drug repurposing, with a specific focus on its relevance amidst the COVID-19 pandemic [15]. Additionally, one Nature article delves into the computational methods employed in drug repurposing, employing AI algorithms to uncover novel applications for approved or investigational drugs.

Among the available datasets, electronic health records (EHRs) offer valuable longitudinal and pathophysiological insight, enabling the effective generation and validation of drug repurposing strategies [18]. Similarly, this approach can be employed for repurposing drugs aimed at treating cancer and AD. Capitalizing on machine learning approaches, researchers can identify and repurpose existing drugs that hold potential efficacy against various forms of cancer. The integration of interpretable deep learning and causal learning can aid in unraveling the intricate biological systems underlying cancer, ultimately revealing novel targets and biomarkers for personalized therapies.

Tyrosine kinase inhibition on the rise

Kinases are a group of enzymes that transfer a phosphate group to a protein, modulating the activities of these proteins. Kinases have garnered significant attention in pharmaceutical research due to their significant influence on a broad range of cellular processes and their potential for treating a wide range of diseases. There are two primary categories of kinases: tyrosine kinases (TKs) and serine-threonine kinases [19]. TKs are divided into distinct subsets known as receptor and non-receptor proteins. Receptor tyrosine kinases (RTKs) encompass noteworthy members such as Platelet-derived growth factor receptors (PDGFR), Fibroblast growth factor receptor (FGFR), Epidermal growth factor receptor (EGFR), and Insulin receptor (IR) [20]. RTKs mediate by facilitating the transmission of signals from outside the cell to the interior cytoplasm (Fig. 3 [21]). These complex proteins are made up of three essential components that play distinct roles in cellular signaling [19]. Extensive oncology research has explored tyrosine kinase pathways and the efficacy of kinase inhibitors (TKIs) based on tumor DNA sequencing. Originally focused on cancer, such as chronic myeloid leukemia (CML) and gastrointestinal stromal tumors via the VEGF pathway, TKIs have transformed malignancy management [19]. Their use has since expanded to include autoimmune disorders and neurodegenerative conditions like Alzheimer's disease (AD) [22].

To review the application of TKIs in AD, it is important to understand their mechanism of action. TKs refer to a group of kinases that facilitate the phosphorylation of tyrosine residues [23]. Firstly, RTKs have an extracellular ligand-binding domain. This domain is situated on the outer surface of the cell and is responsible for interacting

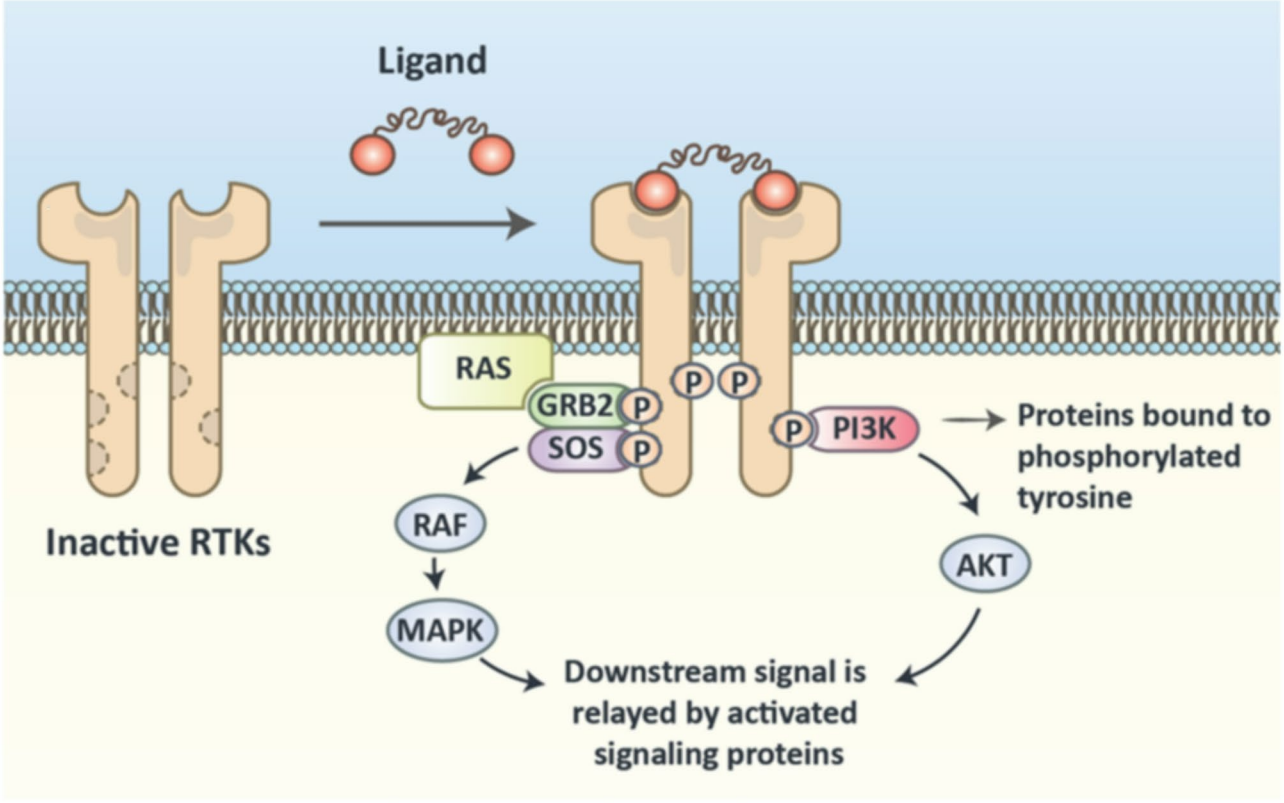

Fig. 3 Receptor Tyrosine Kinase (RTK) domains and activation process. RTKs are being investigated as therapeutic targets for neurodegenerative diseases such as AD. This graphic depicts RTK activation by their specific ligands followed by dimerization of RTKs. Intracellularly, autophosphorylation and phosphorylation of proteins attached to the intracellular domain of tyrosine activates downstream signaling.
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with specific molecules present in the external environment. The external nature of RTKs has allowed for the development of monoclonal antibodies designed to prevent signaling via this extracellular domain [23]. When ligands bind to the receptor, they initiate a cascade of reactions that ultimately transmit signals to the interior of the cell. Secondly, RTKs possess an intracellular catalytic domain that is crucial for carrying out tyrosine kinase activity. Drug developers have exploited the intracellular catalytic domain for the development of specific TK small molecule inhibitors used heavily for cancer, particularly for hormone receptor-positive breast cancers that have become resistant to hormonal antagonists.

Lastly, RTKs include a transmembrane domain that connects both the ligand-binding and catalytic regions. This domain contains a disulfide bond, forming a stable connection between the extracellular and intracellular portions of the receptor. Through this transmembrane domain, signals initiated by ligand binding can be transmitted across the cell membrane, activating downstream signaling pathways in the cytoplasm [20]. In summary, RTKs possess a sophisticated structure comprising an external domain that binds to specific ligands, an internal domain responsible for kinase activity and regulation, and a transmembrane domain that facilitates signal transmission between the external and internal compartments (Fig. 3 [21]).

Non-receptor tyrosine kinases (NRTKs), unlike RTKs that are membrane-bound and interact with extracellular ligands, function intracellularly. The activation of NRTKs involves the phosphorylation of specific tyrosine residues, which in turn modulates downstream signaling pathways and influences various cellular responses [20]. NRTKs display significant diversity in their structural composition, characterized by the presence of a kinase domain and various protein-protein interacting domains such as SH2, SH3, and PH domains [24, 25]. These domains allow NRTKs to interact with other proteins and mediate crucial signaling events within cellular processes [24]. NRTKs play essential roles in numerous physiological processes, including cell growth, differentiation, and survival. NRTKs can also control gene activity, such as the activation of the signal transducer and activator of transcription (STAT) through IL-6-induced phosphorylation of the membrane-bound TK, Janus kinase [26]. The targeted inhibition of NRTKs, like the tyrosine kinase inhibitor nilotinib, represents a valuable therapeutic strategy for diseases driven by dysregulated tyrosine kinase activity, such as certain types of cancers [20].

Nilotinib overview

Nilotinib (Tasigna®, AMN107) is a BCR-ABL tyrosine kinase inhibitor originally developed for the treatment of CML patients who either demonstrated resistance or intolerance to imatinib [27, 28]. Nilotinib has shown considerable efficacy and has significantly improved patient outcomes in the management of CML [29]. Nilotinib was shown to have greater potency in CML cell lines and demonstrated consistent efficacy in 32 out of 33 imatinib-resistant BCR-ABL mutant cell lines [30].

BCR-ABL is a fusion protein linked to specific types of cancer, mainly CML. It forms when the Abelson (Abl) tyrosine kinase gene on chromosome 9 merges with the breakpoint cluster region (Bcr) gene on chromosome 22^{31}. When these genes combine, the BCR-ABL protein remains constantly active, causing uncontrolled growth and multiplication of cells. To counteract this abnormal signaling that fuels cancer growth, inhibiting the activity of BCR-ABL is crucial [32]. Like imatinib, nilotinib exerts its pharmacological effects by selectively inhibiting the activity of BCR-ABL by binding to the ABL kinase domain and preventing the enzyme from phosphorylating tyrosine residues on other proteins [29]. Through its targeted inhibition of BCR-ABL, nilotinib disrupts the aberrant signaling pathways that lead to uncontrolled cellular proliferation in cancer cells.

Nilotinib use in neurodegenerative diseases

Abl kinase inhibition by nilotinib has been proposed as a potential disease-modifying therapy for synucleinopathies like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) [33]. Nilotinib promotes the elimination of α-synuclein by enhancing autophagy, a critical cellular process responsible for clearing misfolded or damaged proteins such as amyloid-beta and phosphorylated tau, key pathological markers in AD [34]. By activating AMPK and inhibiting PP2A, nilotinib restores proteostasis, reducing toxic protein aggregates that disrupt neuronal function. These mechanisms, demonstrated in preclinical AD models, highlight nilotinib's potential as a disease-modifying therapy, targeting fundamental pathological processes in AD [33] and restoring homeostatic processes [35] (Fig. 4 [36]).

There have been various studies testing nilotinib in preclinical models of PD and DLB. In one group, researchers found, when using a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity model of parkinsonism, that nilotinib prevented dopaminergic cell death and behavioral deficits [37]. In another study, Hebron et al. [38] found that nilotinib degraded a-synuclein in PD and in other a-synuceinopathies. In yet another preclinical study of PD, investigators found that nilotinib had anti-inflammatory effects and protected dopaminergic neurons from activated microglia-induced inflammatory damage by suppressing NF-kB signaling [39]. However, it should be noted that nilotinib can not only reduce inflammation, but in some contexts, it can also trigger inflammation.

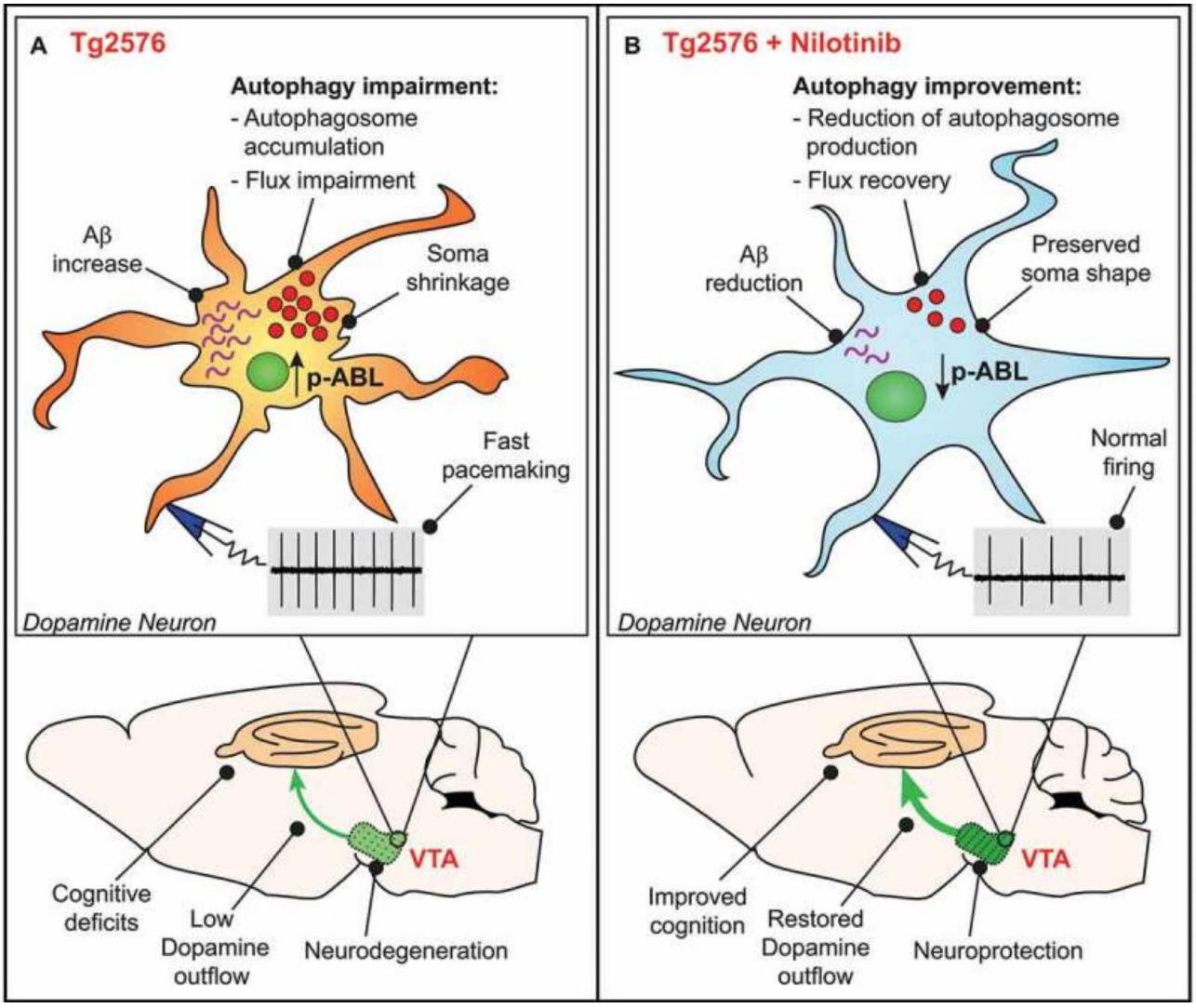

Fig. 4 Neuroprotective effects of nilotinib in Tg2576 mice by improving autophagic flux in VTA dopaminergic neurons, a pathway involved in cognition and motivation. (**A**) Tg2576 mice with impairment in autophagy, leading to decreased dopamine levels, cognitive deficits, and neurodegeneration. (**B**) Tg2576 mice treated with nilotinib, leading to enhanced autophagy function and restored dopamine levels, improved cognitive abilities, and neuroprotective effects.

Adapted from "Targeting autophagy as a therapeutic strategy to prevent dopamine neuron loss in early stages of Alzheimer disease" by A. Nobili et al., 2021, Taylor & Francis, 17(5), 1278–1280. Adapted with permission from Taylor & Francis Ltd, available on https://www.tandfonline.com/doi/full/https://doi.org/10.1080/15548627.2021.1909409.

For example, in a study in CML patients, nilotinib was pro-inflammatory [40].

Another study demonstrated how nilotinib reduced the levels of α-synuclein and phosphorylated tau in the brains of mice that were overexpressing α-synuclein [22]. This treatment increased brain dopamine and showed improvements in the motor skills and cognition of the animals [22].

It is important to note that nilotinib does not exhibit inhibitory effects on serine-threonine kinases (STKs), distinguishing its specificity towards tyrosine kinase inhibition [41]. By precisely modulating the activity of tyrosine kinases, nilotinib offers a promising therapeutic mechanism for combating tyrosine kinase-driven diseases [41]. It is also noteworthy that some TKIs, such as nilotinib, dasatinib, and bosutinib are relatively effective at penetrating the blood-brain barrier [42], suggesting another potential use for treating neurological diseases. In pharmacokinetic studies, nilotinib penetrated the blood-brain barrier and efficiently targeted c-Abl and discoidin domain receptors [43].

Similarly, nilotinib has been investigated for its potential to modulate AD pathology [44]. Researchers from Georgetown University highlighted significant reductions in cerebrospinal fluid (CSF) amyloid and p-tau levels, as well as a noteworthy decrease in hippocampal

volume loss, among patients with AD who received nilotinib compared to those administered a placebo [44]. A single-center, phase II, randomized, double-blind, placebo-controlled study completed in 2020 concluded that up to 12 months of treatment with nilotinib (150 mg/day for 26 weeks followed by 300 mg/day for 26 weeks) was safe, tolerable, and effective in patients with mild to moderate AD. Nilotinib-treated patients exhibited reduced amyloid pathology in the frontal lobe, CSF levels of Aβ40 and Aβ42, and phospho-tau-181, as well as sparing of hippocampal volume [45]. These results from the phase II trial led to the approval of a larger, longer multicenter phase III study that was scheduled to being in February 2022, using two lower doses of nilotinib (84 or 112 mg/day for 72 weeks) [46].

Another particularly noteworthy study aimed to investigate the effects of nilotinib on astroglia derived from the brains of 3xTg-AD mice, a transgenic mouse model of AD [47]. The study's purpose was to determine whether nilotinib can target cellular mechanisms associated with mitochondrial dysfunction, which is believed to play a critical role in AD [2]. Nilotinib-treated astroglia from 3xTg-AD mice demonstrated increased oxygen consumption rate (OCR), ATP production, cytochrome C oxidase (COX) activity, and Mfn1 levels, suggesting an improvement in mitochondrial function [47]. This study represents a significant advancement in our understanding of the potential therapeutic benefits of nilotinib in the context of AD treatment. The findings not only demonstrate a favorable impact of nilotinib on improving mitochondrial function, but also provide compelling evidence supporting the concept that astroglia could serve as a pivotal target for therapeutic interventions in AD. This shows the capacity of nilotinib to enhance astroglial mitochondrial function in a transgenic mouse model of AD which implies that directing nilotinib towards astroglia may have the potential to ameliorate mitochondrial function within the brain; strengthening neuronal health and functionality. Nilotinib may have the potential to alleviate the deleterious effects of mitochondrial dysfunction on neuronal activity, potentially impeding the advancement of neurodegenerative conditions like AD.

These discoveries offer promising insights from preclinical studies and the PD field into the development of novel strategies aimed at mitigating the pathogenesis of AD and enhancing the prospects of efficiently managing this debilitating neurodegenerative disorder, though no clinical trials have yet been conducted in AD.

Moreover, research findings indicate that nilotinib exhibits the capacity to activate AMPK and inhibit PP2A, leading to the stimulation of autophagy in hepatocellular carcinoma (HCC) cell lines and subsequent cell death in xenograft tumor models [48]. Fascinatingly, emerging evidence links nilotinib and autophagy in various scenarios. Notably, studies highlight that nilotinib treatment, in conjunction with an AMPK activator, can enhance LC3 cleavage [48]. These intriguing connections suggest a potential role for nilotinib-induced autophagy in AD research and warrant further investigation in exploring its therapeutic implications for this neurodegenerative condition.

Nilotinib adverse events (AE)

The safety, tolerability, and efficacy of nilotinib were assessed through reported adverse events (AEs), electrocardiograms (ECGs), cognitive and behavioral evaluations, and laboratory tests. In one study, these factors were measured in participants with Alzheimer's Disease (AD) from baseline to 6 months (150 mg nilotinib vs. placebo) and 12 months (300 mg nilotinib vs. placebo) [45]. No serious adverse events (SAEs) such as rhabdomyolysis, bronchitis, vertigo, psychosis, or hypertension were observed in the nilotinib group, while 25% of SAEs were noted in the placebo group [45].

Additional assessments such as electrocardiograms (ECGs) were carried out to evaluate the safety of nilotinib. No corrected QT (QTc) prolongation or other cardiovascular disease was observed in the nilotinib group vs. the placebo group. Moreover, suicide risks and depression were assessed in AD participants with no significant differences observed in the nilotinib group vs. the placebo group. Overall, no significant differences between the nilotinib and placebo groups were found on cognitive, functional, and behavioral outcomes suggesting that a larger, longer, and multicenter study must be adequately powered to test the safety and efficacy of nilotinib in AD.

Moreover, the pharmacokinetics of nilotinib in AD individuals was measured to evaluate whether nilotinib enters the central nervous system. Plasma and cerebrospinal fluid (CSF) levels of nilotinib were monitored at baseline, 6 months, and 12 months. At the 150 mg daily dosage, Cmax was found to be 1,099 nM in plasma and 3.46 nM in CSF, while at the 300 mg daily dosage, Cmax was 1,410 nM in plasma and 4.7 nM in CSF [45].

In discussing the adverse events associated with higher doses of nilotinib, specifically the 300 mg dose, it is important to consider differences in disease pathology and pharmacokinetics between PD and AD. While 150 mg may not provide sufficient benefit in PD, studies show that 300 mg leads to slightly better effects in this population [45]. Turner et al. [45] proposed that due to potential differences in disease pathology, including gut-related factors or interactions with concurrent medications, nilotinib plasma levels are higher in AD patients than in PD patients. This may explain why a lower dose, such as 150 mg, could achieve greater relative efficacy in AD while potentially reducing adverse events. This

further emphasizes the need for deeper investigation into disease-specific dosing strategies to optimize the therapeutic potential of nilotinib in AD.

However, as with any treatment method for any medical condition, one must consider the risks of undergoing said therapy. The potential use of nilotinib for AD is no exception. Among its users, nilotinib has been reported to cause the following adverse events (AEs): fatigue, headaches, nausea, vomiting, diarrhea, edema, mood swings, and sudden cardiac death (SCD) [45, 49]. Researchers recently conducted an up-to-date review regarding TKIs and noted several of the following: compared to its target-specific counterparts like bevacizumab, nilotinib has multiple molecular targets that lead to a greater likelihood of adverse non-target reactions [49]. Given the positive correlation between the number of kinases a TKI inhibits and the drug's toxic effects, it is essential to closely examine nilotinib's potential adverse effects [49]. Furthermore, a twelve-month phase 2 trial revealed that although nilotinib reduced AD biomarkers, such as CSF Aβ42, CSF Aβ40, p-tau, relative to the control group, the drug treatment group had higher diarrheal incidences [45]. One possibility was an interaction between nilotinib and other drugs, such as acetylcholinesterase inhibitors [45]. Therefore, while nilotinib's benefits against AD have been shown in both animal and human studies, researchers and policymakers must not be hasty in promoting the drug for this condition without fully understanding its potential complications.

Additionally, along with imatinib and sunitinib, nilotinib is indicated to have a link with glucose metabolism [49]. The ENESTfreedom trial - a single-arm, phase 2 study - found that 39.5% of individuals in the consolidation phase experienced elevated glucose levels when taking nilotinib [50]. Thus, caution is necessary in patients with or without glycemic issues when using the TKI. Other notable elevations observed during the phase 2 study were alanine aminotransferase (ALT) and bilirubin [50], as well as a potential for increased risk of cardiovascular events such as ischemic heart disease or peripheral vascular disease with long-term use of the drug [51]. Another side effect of nilotinib is an elevated risk of hypophosphatemia, which tends to be persistent and occurs at an earlier stage than other AEs [49].

Moreover, the dosage is another factor to consider. Researchers revealed that mood swings were significantly more frequent with the 300 mg dosage of nilotinib, whereas 150 mg held no difference in AEs compared to the placebo [45]. A retrospective cohort study in South Korea further supports the dosage impact, finding that dosages ≥ 300 mg had a 3.5-fold greater risk of developing hepatotoxicity than dosages < 300 mg [52]. As stated before, the elevations in ALT, bilirubin, and glucose in the ENESTfreedom trial occurred in its consolidation period, where patients received doses of nilotinib ranging from 400 mg to 600 mg [50]. Similarly, the treatment's duration must also be taken into consideration. Data from the ENESTfreedom trial's five-year follow-up revealed that patients who retook nilotinib due to loss of mismatch repair experienced more adverse events [51]. For instance, patients in the re-initiation phase had a 12.5% and 13.6% increase in cardiovascular events and rising blood cholesterol, respectively, compared to those in the consolidation phase [51].

Patient characteristics influencing the safety and efficacy of nilotinib

Simultaneously, the physiology between biological males and females differs, leading to varied pharmacokinetics and pharmacodynamics. These differences can lead to one biological sex experiencing a particular AE more profoundly when compared to the other sex. During the ENESTfreedom trial, female patients with CML (33%) experienced more musculoskeletal pain-related symptoms than their male counterparts (18.8%) after stopping nilotinib usage [50]. In another study utilizing multiple machine-learning approaches, male patients were found to be at a 2.3-fold higher risk of developing hepatotoxicity than females when taking nilotinib [52]. A multicenter retrospective study in Vietnam found that, when using nilotinib as a second-line therapy, females had statistically significantly higher symptom scores than males in fatigue, dyspnea, appetite loss, and insomnia [53].

Researchers also speculated on genetic and biological grounds as to why CML-afflicted females experienced a lower quality of life (QoL) than similarly affected males [53]. A study published in 2017 showed that when orally administered with nilotinib, healthy female C57BL6 mice exhibited a significantly lower number of primary follicles and irregular ovarian structure. The nilotinib-treated male mice, on the other hand, displayed no difference from their control counterparts in either spermatogenic activity or morphologically [54].

Regarding remission rates between nilotinib-treated males and females, the ENESTfreedom trial's treatment-free remission (TFR) phase showed that 53.1% of patients remaining after 48 weeks were females, while only 46.9% were males [50]. Among the 190 patients who entered the TFR phase, 94 and 96 were female and male, respectively [50]. Approximately 55% of females remained in TFR, while 47.9% of males achieved the same result [50]. However, upon conducting a multivariate logistic regression analysis, biological sex was revealed to not be a strong predictor for TFR [50]. Nevertheless, this finding could encourage future studies to investigate the differences in remission rates between biological sexes, particularly considering additional factors such as ethnicity and diet.

Despite these findings, there is still a lack of insight regarding sex differences in nilotinib administration, especially in the context of AD. Furthermore, there is conflicting information regarding nilotinib's effects on males and females. A cross-sectional study on 121 CP-CML patients revealed that the QoL between males and females taking TKIs, which included nilotinib, was not dissimilar [55]. This finding contradicts the previously mentioned, more recent publication in Vietnam that CML-afflicted females suffer a poorer QoL than their male counterparts when taking nilotinib [53]. Another conflicting report is a 2021 study, where researchers assessed the drug's biological effect on mice and found that both sexes were affected, in contrast to the earlier finding that nilotinib did not affect male mice [54, 56]. More specifically, males had significant testicular damage by the Johnsen criteria, while female mice's primordial follicles significantly decreased [56]. Moreover, the control mice had higher pregnancy rates than their nilotinib-treated counterparts of both sexes [56].

It is also important to note gender bias in Alzheimer's research as it is a crucial issue that begs further attention. Historically, research and clinical trials in AD have predominantly focused on male participants, leading to a lack of understanding regarding potential sex-specific differences in disease progression and treatment, despite the rise in female patients being impacted by AD [57–59]. Given the known physiological and hormonal differences between males and females, it is essential to consider the impact of gender on disease manifestation and treatment efficacy. By acknowledging and addressing gender bias in AD research, we can strive for tailored treatment strategies in both male and female patients.

Aside from sex or gender differences, other factors deserve closer attention. While increasing age is linked with poorer QoL, the 4-point decline in QoL from middle-aged patients (40–59 years) to old (≥ 60 years) was not statistically significant, in contrast to the decrease from young-aged adults (18–39 years) to middle-aged [53] in the aforementioned study. Researchers reasoned that the cause of this phenomena was middle-aged adults' inability to fulfill societal expectations and personal responsibilities, leading to another avenue for future nilotinib studies [53]. Another area would be drug's impact on different racial groups or ethnicities. While researchers did observe nilotinib's benefits in AD-afflicted individuals, the patient composition mainly consisted of white individuals [45]. In using a more diversified patient composition, researchers could better assess how the drug impacts various groups. Overall, there remains a greater need to understand nilotinib's difference in effects and outcomes on different patient populations before its potential approval for use against AD.

Summary from meta-analyses

As discussed above, specific preclinical studies and also patient data focusing on the safety, tolerability, and efficacy of TKIs have showed many benefits. However, some recent meta-analyses have also pointed out some outcome limitations of specific TKIs and also differences in efficacy among the TKIs that need further discussion.

For example, to assess the efficacy and tolerability of front-line treatments for patients with newly diagnosed CML, a multiple-treatments meta-analysis was performed by Tang et al. [60] in 2019. In this analysis, 21 randomized controlled trials compared 15 different interventions for chronic-phase CML patients and several conclusions were made. Firstly, nilotinib (300/400 mg BID), dasatinib (100 mg QD) and radotinib (300 mg BID) proved to be the most recommended front-line treatments with the greatest efficacy and tolerability for chronic-phase CML patients [60]. However, high-dose therapies were recommended only for patients in accelerated phase/blast phase or with suboptimal CML-CP response. Finally, it was recommended that the management of adverse events should avoid compromising the clinical efficacy [60].

Moreover, in a 2020 systematic review by Vener et al. [61], the efficacy and safety of imatinib vs. second-generation (dasatinib, nilotinib, bosutinib) and third-generation TKIs (ponatinib) in adults with newly diagnosed Ph + chronic-phase CML, concentrating on progression-free survival, and hematological and nonhematological adverse events were studied. In this analysis, 19 relevant studies plus 15 relevant abstracts (corresponding to 7 randomized controlled trials) were evaluated, and conclusions were generated. These conclusions were as follows: patients with newly diagnosed chronic-phase CML without comorbidities should receive second- or third-generation TKIs; however, on the basis of toxicity outcomes, patients with comorbidities should be treated with imatinib. The use of imatinib was further supported by the current availability of a cheaper generic imatinib [61].

In a recent meta-analysis in 2022 by Xie et al. [62], nilotinib was evaluated to determine the outcomes of different doses in patients with Parkinson's Disease (PD). In this study, three randomized clinical trials were examined that compared two doses. The major conclusion was that the study demonstrated favorable tolerability and safety of the different doses of nilotinib, and improvement in CSF biomarker levels of 300 mg nilotinib. However, the drug also showed poor efficacy on motor outcomes that indicated that nilotinib had no advantages in the clinic for PD [62].

Conclusions

This paper explores the potential usage of nilotinib in attenuating neurodegeneration in AD. Created as a TKI for CML, nilotinib continues to show great promise in preclinical models of both Parkinson's disease as well as AD. Through groundbreaking studies, it has been demonstrated that nilotinib effectively enhances autophagy and inhibits the Abl kinase enzyme, thereby promoting the elimination of α-synuclein and phosphorylated tau. These proteins are pivotal in the development of neurodegenerative diseases. Remarkably, this treatment has shown significant improvements in motor skills, cognition, and the reduction of α-synuclein and tau pathology in animal models. As with any treatment, it is imperative to consider the sex differences as well as potential toxicity. For nilotinib it has been shown that careful dosage adjustments and monitoring may be necessary to minimize adverse effects and maximize the safety and tolerability of nilotinib in future studies. Additionally, larger, longer, and multicenter studies are needed to adequately evaluate the safety and efficacy of nilotinib in AD. While there are not yet definitive conclusions in its efficacy in AD treatment, the investigation into the potential of nilotinib demonstrates a beacon of hope for developing effective, disease-modifying therapies in AD and possibly other neurodegenerative ailments. By embracing personalized medicine approaches that encompass considerations of gender differences and individual patient characteristics, we have the potential to establish the foundation for revolutionary advancements in the treatment of these debilitating neurodegenerative conditions.

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Author contributions
BCA conceived of the review paper. DT and MF led the writing efforts and supplied the figures. BCA, LR, AA, and JL supplied comments and edits and directed the focus and scope of the paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Abeysinghe A, Deshapriya R, Udawatte C. Alzheimer's disease; a review of the pathophysiological basis and therapeutic interventions. Life Sci Sep 1. 2020;256:117996. https://doi.org/10.1016/j.lfs.2020.117996.
2. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. Mar 2021;17(3):327–406. https://doi.org/10.1002/alz.12328
3. Adlimoghaddam A, Roy B, Albensi BC. Future trends and the economic burden of dementia in Manitoba: comparison with the rest of Canada and the world. Neuroepidemiology. 2018;51(1–2):71–81. https://doi.org/10.1159/000490414.
4. Cai W, Wu T, Chen N. The Amyloid-Beta clearance: from molecular targets to glial and neural cells. Biomolecules Feb. 2023;7(2). https://doi.org/10.3390/biom13020313.
5. Yarns BC, Holiday KA, Carlson DM, Cosgrove CK, Melrose RJ. Pathophysiology of Alzheimer's disease. Psychiatr Clin North Am Dec. 2022;45(4):663–76. https://doi.org/10.1016/j.psc.2022.07.003.
6. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clin Med (Lond) Jun. 2016;16(3):247–53. https://doi.org/10.7861/clinmedicine.16-3-247.
7. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in alzheimer disease: an update. J Cent Nerv Syst Dis. 2020;12:1179573520907397. https://doi.org/10.1177/1179573520907397.
8. Sebastião A. Alzheimer's Disease (AD) - Current Treatments. BioRender. p. Visualization of current drugs (Donepezil, Rivastigmine, Galantamine, Memantine) mechanism of action for Alzheimer's Disease (AD).
9. Thomas SJ, Grossberg GT. Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. Clin Interv Aging. 2009;4:367–77. https://doi.org/10.2147/cia.s6666.
10. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PLoS ONE. 2015;10(4):e0123289. https://doi.org/10.1371/journal.pone.0123289.
11. Hoy SM, Lecanemab. First approval. Drugs Mar. 2023;83(4):359–65. https://doi.org/10.1007/s40265-023-01851-2.
12. Loeffler DA. Antibody-Mediated clearance of brain Amyloid-beta: mechanisms of action, effects of natural and monoclonal Anti-Abeta antibodies, and downstream effects. J Alzheimers Dis Rep. 2023;7(1):873–99. https://doi.org/10.3233/ADR-230025.
13. Low ZY, Farouk IA, Lal SK. Drug repositioning: new approaches and future prospects for Life-Debilitating diseases and the COVID-19 pandemic outbreak. Viruses Sep. 2020;22(9). https://doi.org/10.3390/v12091058.
14. Ballard C, Aarsland D, Cummings J, et al. Drug repositioning and repurposing for alzheimer disease. Nat Rev Neurol Dec. 2020;16(12):661–73. https://doi.org/10.1038/s41582-020-0397-4.
15. Yang F, Zhang Q, Ji X, et al. Machine learning applications in drug repurposing. Interdiscip Sci Mar. 2022;14(1):15–21. https://doi.org/10.1007/s12539-021-00487-8.
16. Judge A, Garriga C, Arden NK, et al. Protective effect of antirheumatic drugs on dementia in rheumatoid arthritis patients. Alzheimers Dement (N Y) Nov. 2017;3(4):612–21. https://doi.org/10.1016/j.trci.2017.10.002.
17. Corbett A, Pickett J, Burns A, et al. Drug repositioning for Alzheimer's disease. Nat Rev Drug Discov Nov. 2012;11(11):833–46. https://doi.org/10.1038/nrd3869.
18. Zong N, Wen A, Moon S, et al. Computational drug repurposing based on electronic health records: a scoping review. NPJ Digit Med Jun. 2022;14(1):77. https://doi.org/10.1038/s41746-022-00617-6.
19. Lahiry P, Torkamani A, Schork NJ, Hegele RA. Kinase mutations in human disease: interpreting genotype-phenotype relationships. Nat Rev Genet Jan. 2010;11(1):60–74. https://doi.org/10.1038/nrg2707.
20. Siveen KS, Prabhu KS, Achkar IW, et al. Role of Non receptor tyrosine kinases in hematological malignances and its targeting by natural products. Mol Cancer Feb. 2018;19(1):31. https://doi.org/10.1186/s12943-018-0788-y.
21. Azad T, Rezaei R, Surendran A, et al. Hippo signaling pathway as a central mediator of receptors tyrosine kinases (RTKs) in tumorigenesis. Cancers (Basel) Jul. 2020;24(8). https://doi.org/10.3390/cancers12082042.
22. Fagiani F, Lanni C, Racchi M, Govoni S. Targeting dementias through cancer kinases Inhibition. Alzheimers Dement (N Y). 2020;6(1):e12044. https://doi.org/10.1002/trc2.12044.
23. Jo DH, Kim JH, Kim JH. Targeting tyrosine kinases for treatment of ocular tumors. Arch Pharm Res Apr. 2019;42(4):305–18. https://doi.org/10.1007/s12272-018-1094-3.
24. Paul MK, Mukhopadhyay AK. Tyrosine kinase - Role and significance in Cancer. Int J Med Sci. 2004;1(2):101–15. https://doi.org/10.7150/ijms.1.101.

25. Schenk PW, Snaar-Jagalska BE. Signal perception and transduction: the role of protein kinases. Biochim Biophys Acta Feb. 1999;4(1):1–24. https://doi.org/10.1016/s0167-4889(98)00178-5.
26. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F. Principles of Interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J Aug. 2003;15(Pt 1):1–20. https://doi.org/10.1042/BJ20030407.
27. Eshraghi M, Ahmadi M, Afshar S, et al. Enhancing autophagy in Alzheimer's disease through drug repositioning. Pharmacol Ther Sep. 2022;237:108171. https://doi.org/10.1016/j.pharmthera.2022.108171.
28. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following Imatinib resistance and intolerance. Blood Nov. 2007;15(10):3540–6. https://doi.org/10.1182/blood-2007-03-080689.
29. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med Mar. 2003;13(11):994–1004. https://doi.org/10.1056/NEJMoa022457.
30. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. Br J Cancer Jun. 2006;19(12):1765–9. https://doi.org/10.1038/sj.bjc.6603170.
31. Sampaio MM, Santos MLC, Marques HS, et al. Chronic myeloid leukemia-from the Philadelphia chromosome to specific target drugs: A literature review. World J Clin Oncol Feb. 2021;24(2):69–94. https://doi.org/10.5306/wjco.v12.i2.69.
32. Cilloni D, Saglio G. Molecular pathways: BCR-ABL. Clin Cancer Res Feb. 2012;15(4):930–7. https://doi.org/10.1158/1078-0432.CCR-10-1613.
33. Werner MH, Olanow CW. Parkinson's disease modification through Abl kinase Inhibition: an opportunity. Mov Disord Jan. 2022;37(1):6–15. https://doi.org/10.1002/mds.28858.
34. Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol May. 2010;221(1):3–12. https://doi.org/10.1002/path.2697.
35. Fellner L, Gabassi E, Haybaeck J, Edenhofer F. Autophagy in alpha-Synucleinopathies-An overstrained system. Cells Nov. 2021;12(11). https://doi.org/10.3390/cells10113143.
36. Nobili A, La Barbera L, D'Amelio M. Targeting autophagy as a therapeutic strategy to prevent dopamine neuron loss in early stages of alzheimer disease. Autophagy May. 2021;17(5):1278–80. https://doi.org/10.1080/15548627.2021.1909409.
37. Karuppagounder SS, Brahmachari S, Lee Y, Dawson VL, Dawson TM, Ko HS. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep May 2. 2014;4:4874. https://doi.org/10.1038/srep04874.
38. Hebron ML, Lonskaya I, Moussa CE. Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of alpha-synuclein in Parkinson's disease models. Hum Mol Genet Aug. 2013;15(16):3315–28. https://doi.org/10.1093/hmg/ddt192.
39. Wu J, Xu X, Zheng L, Mo J, Jin X, Bao Y. Nilotinib inhibits microglia-mediated neuroinflammation to protect against dopaminergic neuronal death in Parkinson's disease models. Int Immunopharmacol Oct. 2021;99:108025. https://doi.org/10.1016/j.intimp.2021.108025.
40. Sicuranza A, Ferrigno I, Abruzzese E, et al. Pro-Inflammatory and Pro-Oxidative changes during nilotinib treatment in CML patients: results of a prospective multicenter Front-Line TKIs study (KIARO study). Front Oncol. 2022;12:835563. https://doi.org/10.3389/fonc.2022.835563.
41. Oruganti B, Lindahl E, Yang J, Amiri W, Rahimullah R, Friedman R. Allosteric enhancement of the BCR-Abl1 kinase Inhibition activity of nilotinib by cobinding of asciminib. J Biol Chem Aug. 2022;298(8):102238. https://doi.org/10.1016/j.jbc.2022.102238.
42. Gong X, Li L, Wei H, et al. A higher dose of dasatinib May increase the possibility of crossing the Blood-brain barrier in the treatment of patients with Philadelphia Chromosome-positive acute lymphoblastic leukemia. Clin Ther Jul. 2021;43(7):1265–e12711. https://doi.org/10.1016/j.clinthera.2021.05.009.
43. Nobili A, D'Amelio M, Viscomi MT. Nilotinib: from animal-based studies to clinical investigation in Alzheimer's disease patients. Neural Regen Res Apr. 2023;18(4):803–4. https://doi.org/10.4103/1673-5374.350700.
44. Teber K. Nilotinib appears safe and affects biomarkers in Alzheimer's disease clinical trial. Georget Univ. 2024. https://gumc.georgetown.edu/news-release/nilotinib-appears-safe-and-affects-biomarkers-in-alzheimers-disease-clinical-trial/#
45. Turner RS, Hebron ML, Lawler A, et al. Nilotinib effects on safety, tolerability, and biomarkers in Alzheimer's disease. Ann Neurol Jul. 2020;88(1):183–94. https://doi.org/10.1002/ana.25775.
46. Evaluating the Efficacy and Safety of Nilotinib BE in Subjects With Early Alzheimer's Disease (NILEAD). National library of medicine. Updated 12/03/2021. Accessed 05/06, 2024. https://clinicaltrials.gov/study/NCT05143528?tab=table
47. Adlimoghaddam A, Odero GG, Glazner G, Turner RS, Albensi BC. Nilotinib improves bioenergetic profiling in brain astroglia in the 3xTg mouse model of Alzheimer's disease. Aging Dis Apr. 2021;12(2):441–65. https://doi.org/10.14336/AD.2020.0910.
48. Yu HC, Lin CS, Tai WT, Liu CY, Shiau CW, Chen KF. Nilotinib induces autophagy in hepatocellular carcinoma through AMPK activation. J Biol Chem Jun. 2013;21(25):18249–59. https://doi.org/10.1074/jbc.M112.446385.
49. Shyam Sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. Signal Transduct Target Ther Jul. 2023;7(1):262. https://doi.org/10.1038/s41392-023-01469-6.
50. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the enestfreedom study. Leuk Jul. 2017;31(7):1525–31. https://doi.org/10.1038/leu.2017.63.
51. Radich JP, Hochhaus A, Masszi T, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the enestfreedom trial. Leuk May. 2021;35(5):1344–55. https://doi.org/10.1038/s41375-021-01205-5.
52. Kim JS, Han JM, Cho YS, Choi KH, Gwak HS. Machine learning approaches to predict hepatotoxicity risk in patients receiving nilotinib. Molecules May. 2021;31(11). https://doi.org/10.3390/molecules26113300.
53. Nguyen CTT, Nguyen BT, Nguyen TTT, Petrelli F, Scuri S, Grappasonni I. Quality of life among chronic myeloid leukemia patients in the second-line treatment with nilotinib and influential factors. Qual Life Res Mar. 2022;31(3):733–43. https://doi.org/10.1007/s11136-021-02952-9.
54. Cengiz Seval G, Ozkavukcu S, Seval M, Ayli M. Gonadotoxic effects of nilotinib in chronic myeloid leukemia treatment dose in a mouse model. Turk J Haematol Jun. 2017;5(2):137–42. https://doi.org/10.4274/tjh.2016.0092. Kronik Miyeloid Losemi Tedavi Dozunda Nilotinib'in Gonadotoksik Etkilerinin Fare Modelinde Gosterilmesi.
55. Bostan H, Toptas T, Tanrikulu FP, et al. Quality of life and symptom burden with First- and Second-generation tyrosine kinase inhibitors in patients with chronic-phase chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk Dec. 2020;20(12):836–42. https://doi.org/10.1016/j.clml.2020.08.009.
56. Ozkavukcu S, Kuscu N, Adiguzel D, Cengiz-Seval G, Celik-Ozenci C. Deleterious reproductive effects of nilotinib in mouse model. Reprod Mar. 2021;161(3):295–306. https://doi.org/10.1530/REP-20-0548.
57. Bonsignore M, Barkow K, Heun R. Possible influence of selection bias on gender differences in the risk of Alzheimer's disease. Arch Womens Ment Health Oct. 2002;5(2):73–7. https://doi.org/10.1007/s00737-002-0144-4.
58. Podcasy JL, Epperson CN. Considering sex and gender in alzheimer disease and other dementias. Dialogues Clin Neurosci Dec. 2016;18(4):437–46. https://doi.org/10.31887/DCNS.2016.18.4/cepperson.
59. Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. Alzheimers Dement Dec. 2022;18(12):2707–24. https://doi.org/10.1002/alz.12662.
60. Tang L, Zhang H, Peng YZ, et al. Comparative efficacy and tolerability of front-line treatments for newly diagnosed chronic-phase chronic myeloid leukemia: an update network meta-analysis. BMC Cancer Aug. 2019;28(1):849. https://doi.org/10.1186/s12885-019-6039-9.
61. Vener C, Banzi R, Ambrogi F, et al. First-line Imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. Blood Adv Jun. 2020;23(12):2723–35. https://doi.org/10.1182/bloodadvances.2019001329.
62. Xie X, Yuan P, Kou L, Chen X, Li J, Li Y. Nilotinib in Parkinson's disease: A systematic review and meta-analysis. Front Aging Neurosci. 2022;14:996217. https://doi.org/10.3389/fnagi.2022.996217.

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