Review

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Galantamine as a Potential Treatment for Peripheral Nerve Injuries: Emphasis on Non-Systemic Delivery

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Abstract

Galantamine, a reversible inhibitor of acetylcholinesterase, exhibits both acetylcholinesterase-inhibiting and neuroprotective properties. The FDA (Food and Drug Administration) and EMA (European Medicines Agency) have approved it for use in the treatment of Alzheimer's disease dementia (AD). The side effects associated with oral administration include gastrointestinal irritation, first-pass hepatic metabolism leading to reduced bioavailability and systemic adverse reactions such as nausea or liver enzyme elevation. These issues have led to the exploration of alternative delivery routes, such as transdermal, intranasal, or buccal. Such routes can bypass the gastrointestinal tract and liver, thereby reducing the risk of digestive discomfort and hepatic strain. The FDA has approved acetylcholinesterase inhibitors, such as rivastigmine, for transdermal administration in the form of patches. Studies on the transdermal administration of galantamine are ongoing. In addition to its use for AD, galantamine is increasingly being investigated for its effects on various conditions, including its potential in treating peripheral nervous system damage. In Bulgaria, a method for depositing galantamine through iontophoresis has been developed and widely used in clinical practice for many years. However, there is a lack of scientific evidence to support its effectiveness according to modern scientific approaches, necessitating further research in this direction.

Keywords: galantamine; transdermal delivery; peripheral nerve damage; non-systemic delivery; nivalin; iontophoresis

1. Introduction

Acetylcholinesterase (AChE) inhibitors modulate the hydrolysis of acetylcholine and increase the level and duration of the neurotransmitter's action [1]. They play a key role in determining cholinergic tone and in exerting their effects on cholinergic blockade of inflammatory processes. According to the mode of action, AChE inhibitors can be divided into two groups: irreversible and reversible. Reversible inhibitors can be competitive or non-competitive and have primarily therapeutic applications, while toxic effects are associated with irreversible modulators of AChE activity [2]. Reversible AChE inhibitors play an important role in the pharmacological manipulation of enzyme activity [3].

Galantamine is a competitive and reversible inhibitor of acetylcholinesterase that works to increase acetylcholine levels [4]. In addition, the drug is an allosteric ligand of nicotinic cholinergic receptors, causing their modulation. It interacts with the nicotinic receptor at binding sites separate from those for ACh and nicotinic agonists, and acts specifically to increase the activity (sensitisation) of nicotinic receptors in the presence of ACh. Galantamine acts both centrally and peripherally to inhibit both muscle and brain acetylcholinesterase, thereby increasing cholinergic tone [5].

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Galantamine, belonging to the group of organic compounds known as galanthamine-type amaryllidaceae alkaloids, is isolated from the plant Galanthus woronowii [3]. In 1951, M. D. Mashkovsky and R. P. Kruglikova-Lvova conducted the first pharmacological studies of galantamine. Galantamine was found to be a natural, highly effective anticholinesterase agent . In 1956, galantamine was also extracted from the common snowdrop – Galanthus nivalis L. (D. Paskov, L. Ivanova, Bulgaria) [2]. Galantamine enhances the intrinsic activity of acetylcholine at nicotinic receptors, probably by binding to an allosteric portion of the receptor. As a result, increased activity of the cholinergic system leads to improved cognitive function in patients with Alzheimer's dementia [6,7].

In the late 1950s, numerous preclinical studies on the pharmacological properties of galantamine revealed that galantamine acts as an antagonist of non-depolarizing neuromuscular blockers. In vivo and in vitro experiments are being conducted in rats to determine the effects of galantamine on the brain [8].

Galantamine was first approved in Iceland, Ireland, Sweden, and the UK for the treatment of Alzheimer's disease in 2000. In 2003, it was approved for use in the US and it is indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type. This indication and the possible adverse drug reactions are well known and proven by the results of various clinical trials (controlled and open, as well as longitudinal studies to monitor the progression of the disease in a specific group of patients).

Galantamine exists as a capsule. The extended-release form is available in different strengths: 8 mg, 16 mg, and 24 mg. Tablets and solutions are the immediate types of drug-delivering systems. The solution contains 4 mg of galantamine per mL, and the tablet form is available in doses of 4 mg, 8 mg, or 12 mg [4].

Acetylcholinesterase inhibitors (AChEIs) are used off-label, in both adults and pediatric patients, to aid in further neurorecovery after traumatic brain injury [9]. Galantamine has been found to mitigate acute toxicity in non-human primates, indicating its potential neuroprotective effects.

Other indications outside the approved ones are: Vascular dementia [10]; Dementia associated with Parkinson disease [10]; Frontotemporal dementia [11]; Galantamine alone or along with memantine is effective in the treatment of cognitive impairment due to traumatic brain injury [12]; positive, cognitive, and negative symptoms of schizophrenia [13]; it alleviates some of the symptoms in children with autism [14]. Galantamine treatment is beneficial in chronic post-stroke aphasia and it is an effective antidote against organophosphorus poisoning [15].

Galantamine has been reported to inhibit oxidative stress and inflammation, which are common in various chronic conditions. This opens up potential uses in treating inflammatory disease [16].

Galantamine has been shown to potentiate neurotransmitter release by blocking small conductance Ca^{2+}-activated K^{+} channels, which could have implications for various neurological conditions [17]. The potential of galantamine to affect various conditions other than Alzheimer's dementia is being studied [5].

The objective of this study is to evaluate the potential of galantamine, when applied topically, to influence damage in the peripheral nervous system.

2. Materials and Methods

This narrative review was conducted through a structured search of multiple scientific databases, including PubMed, Google Scholar, EBSCO, MDPI, Cochrane Library, SpringerLink, and ScienceDirect. The primary focus was on literature related to galantamine, with emphasis on non-systemic administration routes, its potential role in peripheral nerve damage, and applications involving iontophoresis. Search terms included combinations of the following keywords: *"galantamine," "Nivalin," "non-systemic administration," "peripheral nerve damage," "iontophoresis,"* and *"acetylcholinesterase inhibitor."* Boolean operators (AND, OR) were used to refine the search.

Inclusion criteria:

- Publications from 2005 to 2025

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- Articles written in English or Bulgarian
- Studies containing clinical or preclinical data on galantamine, including those using its trade name Nivalin
- Relevant research on galantamine's mechanism of action, delivery methods, and therapeutic applications for nerve damage

Exclusion criteria:

- Studies focused solely on other acetylcholinesterase inhibitors
- Publications outside the defined timeframe or in languages other than English/Bulgarian
- Irrelevant topics not directly connected to galantamine or its peripheral application

Additional Data Sources

The review also includes analysis of national clinical guidelines approved for funding by the National Health Insurance Fund (NHIF) in Bulgaria related to the treatment of peripheral nerve damage. Furthermore, publicly accessible data from the NHIF were reviewed to assess the reimbursement and use of galantamine in outpatient care during the period 01.01.2025 to 31.03.2025.

Limitations

Due to the limited availability of recent and specific data, particularly concerning non-systemic use and peripheral indications, historical and archival sources—including paper-based materials dating back to 1959—were consulted to support the review. These sources were critically assessed for relevance and credibility.

3. Results

3.1. Clinical Applications of Galantamine in Bulgaria

A study of the effect of galantamine after experimental sciatic nerve injury (SCI) in rats demonstrated that pharmacological intervention with galantamine demonstrated a protective effect on degeneration after peripheral nerve injury, but studies in the field are scarce [2].

In Bulgaria, two tablet forms are available: 5 mg (60 tablets) and 10 mg (20 tablets), and ampoule forms: 2.5 mg/1 ml, 5 mg/1 ml, 10 mg/1 ml. As of March 2025, according to NHIF data, only 9 patients in Bulgaria use Galantamine for the treatment of Alzheimer's dementia. Use the tablet and ampoule forms for the treatment of polyradiculoneuritis, radiculoneuritis, neuritis, polyneuritis, polyneuropathies [17]. It is used in conditions associated with damage to the anterior horns of the spinal cord (after poliomyelitis, myelitis, spinal muscular atrophy); cerebral palsy (conditions after stroke, infantile cerebral palsy); neuromuscular synapse disorders (myasthenia gravis, muscular dystrophy) [18]; anesthesiology and surgery - to eliminate the Effect of non-depolarizing neuromuscular blockers and to treat postoperative paresis of the small intestine and bladder; physiotherapy physiotherapy - iontophoretic for neurological damage to the peripheral nervous system, nocturnal enuresis [19].

According to the guidelines in the country, treatment for all acute neuritis and neuropathies begins immediately, within the first 10-15 days, with Galantamine as the second choice, administered on a schedule. Plexitis is treated with Galantamine i.m. according to a scheme, vitamins of group B (B1-30 mg, B6-0.1 g, B12-1000 μg daily intramuscularly) and physiotherapy. In case of sensory and motor symptoms, cholinergic drugs can be used (Galantamine according to an ascending-descending scheme for 30-90 days) [20]. According to official data released by the National Health Insurance Fund for the period 01.01-31.03.2025, galantamine tablets (5mg and 10mg) were most frequently prescribed for the treatment of diabetic polyneuropathy G 63.2 81,16% ; N= 1221 of patients; G 54.4 Lumbosacral root disorders, not elsewhere classified 7.75%; N=117 and G 54.1 Lumbosacral plexus disorders 4,77% ; N=72 [19].

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3.2. Alternative Delivery Methods

Oral administration of medicinal products containing galantamines leads to gastrointestinal issues: The most frequently reported side effects include nausea (20%), vomiting (10%), and diarrhoea (5-7%). These effects are likely due to galantamine's action on the gastrointestinal tract, causing disturbances in motility and smooth muscle contractions. Studies have shown that galantamine affects gastric myoelectric activity, which may explain gastrointestinal side effects in humans. As a prodrug, benzgalantamine is absorbed from the intestine unchanged and then metabolized into the active form: galantamine. Another common side effect is dyspepsia. Galantamine has been shown to negatively affect gastric myoelectric activity, which could explain the dyspepsia observed in some patients. Mild side effects such as headache and appetite suppression have also been reported [21].

While galantamine can improve cognitive functions in Alzheimer's patients, it can also cause side effects such as anxiety, agitation, and hallucinations. In some cases, it has been associated with nightmares and anxiety, particularly with rapid dose titration 8. Motor Symptoms: In patients with Parkinson's disease, galantamine has been associated with worsening of motor symptoms and gastrointestinal side effects, leading to a high dropout rate in clinical trials [22] .

Other Side Effects: Drooling and Postural Hypotension: These side effects have been observed in a subset of patients, along with nausea and dysuria 3. Sleep Disturbances: Some patients have reported improvements in sleep, while others experienced sleep-related issues such as nightmares.

Comparison between the oral and intranasal routes of galantamine (GLT) confirms that adverse effects associated with the oral route are due to interaction in the gastrointestinal tract and not to systemic exposure of the drug . To avoid gastrointestinal side effects associated with oral administration, intranasal delivery of galantamine using chitosan-based nanoparticles has been explored. This method could provide a more patient-friendly and efficient delivery system

Another method under development is the buccal administration of galantamine [23].

Transdermal and intranasal delivery of galantamine represent promising alternatives to oral administration, with demonstrated benefits in avoiding systemic side effects and potentially enhancing patient compliance [24].

For the treatment of Alzheimer's disease (AD), the FDA has approved transdermal patches containing acetylcholinesterase inhibitors, such as donepezil and rivastigmine. Donepezil patches are replaced weekly [25], while rivastigmine patches are replaced daily. These patches have been shown to improve cognitive symptoms within a short period and minimize drug interactions [26].

Research, both in vitro and in vivo, has been conducted to identify the most suitable form for transdermal administration, including studies on gel formulations and the characteristics of transdermal systems. It was initially found that the free form of galantamine is more readily absorbed during transdermal administration, posing a challenge since galantamine hydrobromide is primarily used [27].

Plasma concentrations of galantamine (GLT) after intravenous administration at a dose of 5 mg/kg decrease rapidly, becoming minimal after 4 hours. Oral administration of GLT is quickly absorbed from the gastrointestinal tract, reaching a maximum concentration (Cmax) of 254.01 ± 16.46 ng/mL at a time to peak concentration (Tmax) of 0.50 ± 0.00 hours (mean ± SD, n = 3). However, these plasma concentrations also decline rapidly and become undetectable after 6 hours. In contrast, after transdermal administration, plasma concentrations of GLT rise quickly, reaching a Cmax of approximately 21.8–112.1 ng/mL, with a Tmax of approximately 2.0–5.6 hours. During the wear time of the patch (up to 12 hours), plasma levels of different GLT patch models remained stable, ranging from 14 to 112 ng/mL, before decreasing until patch removal at 24 hours [28].

In a study to monitor the effect of galantamine administered transdermally on rheumatoid arthritis (RA), RA was induced in Sprague-Dawley rats through intradermal injection. The rats received oral growth hormone (GH) at 1.25 mg/kg/day and a transdermal GH patch at 2.5 mg/kg every 2 days for 14 days, during which hindpaw swelling and body weight (BW) were assessed [29]. The study evaluated the effects on C-reactive protein (CRP), inflammatory cytokines (TNF-α, IL-10, and IL-1β), and Janus kinase (JAK-2). Both oral and transdermal GH treatments significantly reduced

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hindpaw swelling in the arthritis model and provided protective effects against RA. However, the oral GH group experienced a significant decrease in body weight compared to the transdermal patch group, which showed a more significant reduction in IL-1β levels than the oral group. There was no significant difference in TNF-α and IL-10 levels between the two treatment groups [29].

According to the studies, the optimal gel formulation for the patch reservoir was found to contain 0.89% w/w carbopol, 1.16% w/w triethanolamine, and 4.19% w/w GH. Optimization analysis indicated that this formulation had a predicted cumulative drug release rate of 17.80 mg·cm² at 8 hours, with a predicted permeation flux of 2.27 mg·cm²/h. These predicted values closely matched the actual cumulative drug release rate (16.93 ± 0.08 mg·cm²) and the actual permeation flux (2.32 ± 0.02 mg·cm²/h) observed in experiments [30].

Scientific studies showed that the optimized patch contained 8% GLT and 3% oleic acid, resulting in high absolute bioavailability (80%) and stable plasma GLT levels over an extended period (24 hours) with these patches.

Preclinical studies have successfully formulated galantamine gel and patch systems, achieving sustained release and adequate bioavailability [28].

3.3.T. he Potential Benefits of Using Galantamine Topically:

The numerous side effects necessitate the search for alternative drug delivery systems and alternative routes of administration, in order to avoid the digestive system and passage through hepatic metabolism. Transdermal administration reduces gastrointestinal side effects [21].

Advantages of transdermal application are: topical administration is non-invasive and can be self-administered, which may improve patient compliance and convenience. Topical application can potentially reduce systemic side effects compared to oral administration. This is particularly relevant for drugs like galantamine, which can cause gastrointestinal side effects when taken orally [31] .

Localized Effect: topical application allows for localized drug delivery, which could be beneficial for treating conditions with localized symptoms or for targeting specific areas, such as in the case of neurodegenerative diseases affecting specific brain regions [32].

Avoidance of first-pass metabolism: topical administration bypasses the liver's first-pass metabolism, potentially increasing the bioavailability of the drug and allowing for lower doses to achieve therapeutic effects.

Potential Neuroprotective Effects: galantamine has demonstrated neuroprotective effects in various studies, including protection against amyloid-β-induced toxicity and peripheral nerve degeneration [10,33]. These properties could be beneficial if the drug can be effectively delivered to the target tissues through the skin.

Studies indicate that by modifying carriers for dermal administration, a systemic effect can be obtained [34]. Transdermal drug delivery systems are expected to improve patient compliance.

Challenges and considerations are skin penetration. The primary challenge for topical administration is the drug's ability to penetrate the skin barrier, particularly the stratum corneum. Enhancers and advanced delivery systems like nanoparticles or vesicles may be required to improve penetration. Formulation: the formulation of the topical preparation is crucial. Factors such as the drug's physicochemical properties, the choice of excipients, and the delivery system can significantly affect the drug's ability to permeate the skin and reach the target tissues .

3.4. Use of Galantamine by Transdermal Deposition in Physiotherapy

Iontophoresis enhances transdermal drug penetration by applying a low-intensity electric current, facilitating the movement of ionized drug molecules through the stratum corneum. This mechanism is particularly advantageous for hydrophilic, ionizable compounds such as galantamine, which exhibit limited passive diffusion across intact skin barriers. Iontophoresis is suitable for drugs that are ionically active (charged particles , as is the case with galantamine [20].

Indications: In conjunction with other therapeutic regimens, galantamine with iontophoresis is indicated for improving neuromuscular conduction in peripheral nervous system damage, aiding in

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the recovery of traumatic plexitis, and has an unblocking effect on traumatic damage to the lumbosacral plexus and its individual nerves (n. sciaticus; n. tibialis; n. fibularis) [35]. Table 1 presents the method used for the introduction of galantamine, by iontophoresis [21].

Table 1. Stages of galantamine administration by iontophoresis.

Parameter	Description
Pharmaceutical Agent	Galantamine hydrobromide – reversible acetylcholinesterase inhibitor
Solution Characteristics	Aqueous solution (0.25%–1%); pH maintained between 5.0–6.0 to optimize iontophoretic transport
Electrochemical Consideration	Galantamine as a cation, is delivered via the anode (positive electrode)
Electrode Placement	Active electrode: target dermal site (e.g., cervical, lumbar, extremities)Passive electrode: contralateral or distal position
Device Parameters	Current intensity: 0.5–5 mA (patient-dependent tolerance)- Application time: 10–20 minutes- Current type: constant direct current (galvanic)
Treatment Regimen	Frequency: Daily or every other day Duration: 10–15 sessions per therapeutic cycle
Clinical Advantages	Minimally invasive transdermal drug delivery- Reduction of systemic gastrointestinal exposure- Potential for localized drug accumulation- Well-suited for patients with hepatic or gastrointestinal contraindications

Iontophoresis with galantamine follows the following administration algorithm: 1. Preparation of the solution - An aqueous solution of galantamine hydrobromide is used. The concentration is usually 0.25–1% (depending on the prescription) according to Yasnogorodsky V.G. 1990 [36]. The pH of the solution is maintained at a slightly acidic to neutral value (pH ~5–6). 2. Selection of electrodes - Galantamine is positively charged (cation), so it is applied under the anode (positive electrode). The active electrode is placed on the skin in the area where local action is desired. The passive electrode is placed elsewhere to close the electrical circuit. 3. Device settings Current: 0.5 – 5 mA, depending on the patient's sensitivity. Duration: 10–20 minutes. Type of current: galvanic (constant). 4. Frequency of procedures. Usually applied daily or every other day, with one course of 10 to 15 procedures [37].

The application may vary depending on the condition. In peripheral neuritis, due to infection, rheumatism, trauma, treatment is allowed after 20 days, Current intensity: 6–16 mA; Duration: 6–16 minutes 20 sessions. In polyneuritis caused by infections; exogenous intoxications, endogenous intoxications; vegetative polyneuritis, colds, longitudinal electrophoresis is performed to prevent connective tissue growths and transverse electrophoresis of the spine. Number of procedures 30-35 with a duration of 10-30 minutes [35].

3.5. Advantages of Using Iontophoresis for Galantamine

The advantages are painless and non-invasive application. Iontophoresis provides a non-invasive alternative to oral or injectable routes, which can be particularly beneficial for patients with swallowing difficulties or those requiring long-term medication [38].

Gastrointestinal irritation is avoided. Allows local accumulation of the medication. Suitable for patients with liver/stomach problems. The technique allows for controlled and sustained drug delivery, which can improve therapeutic outcomes and reduce side effects associated with

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fluctuating drug levels [39,40]. Iontophoresis significantly enhances the permeation of galantamine through the skin or mucosa, overcoming barriers that limit the effectiveness of conventional delivery methods [40].

Contraindications for this therapy include skin lesions at the site of application, tumor processes, pregnancy (with caution), a pacemaker, metal implants in the area.

4. Discussion

The findings from the reviewed literature and policy documents suggest that galantamine has potential clinical utility beyond its established role in cognitive disorders. While its systemic use in Alzheimer's disease is well-documented and approved in multiple countries, its historical and current use in Eastern Europe—particularly in Bulgaria—includes indications such as peripheral nerve damage. This broader therapeutic application appears to be underexplored in modern Western literature, yet supported by decades of clinical experience in Bulgaria.

When administered orally, galantamine has adverse drug reactions that compromise compliance and adherence to therapy. As a result, alternative routes of administration, such as non-systemic and dermal administration, are of increasing interest. Iontophoresis, in particular, has shown promise as a technique for enhancing transdermal absorption of galantamine without the need for invasive procedures or oral dosing. However, robust clinical evidence in this area remains scarce and largely preclinical or anecdotal.

The Bulgarian clinical context offers a unique case study. Galantamine is still used for peripheral nerve recovery, and its inclusion in NHIF-funded treatment protocols demonstrates its continued relevance in national healthcare. Notably, data from the first quarter of 2025 show active reimbursement for outpatient treatment with galantamine, which may reflect both physician confidence in its efficacy and its availability within the public health system. However, the lack of recent high-quality randomized controlled trials (RCTs) or modern pharmacokinetic studies in the context of non-systemic application highlights a significant evidence gap.

Another limitation is the reliance on historical and paper-based data, some dating back as far as 1959. While these sources provide valuable insight into long-term clinical practices, they do not always meet current standards for evidence-based medicine. The absence of harmonized international guidelines for the use of galantamine in peripheral nerve disorders further underscores the need for updated research, including modern delivery methods such as iontophoresis and comparative studies with other neuroregenerative agents.

Overall, while preliminary evidence and historical usage support the feasibility of galantamine in treating peripheral nerve damage—especially via non-systemic delivery—the current literature is insufficient to support broad clinical recommendations. Further studies are needed to evaluate its safety, efficacy, and pharmacodynamics when applied locally, as well as its cost-effectiveness in national health systems.

Despite the continued use of the methodology in the rehabilitation of large groups of patients with peripheral nervous system damage, there is a need for clinical trials on modern medical approaches. There is a lack of clinical data specifically evaluating the efficacy and safety of topical galantamine. More research is needed to establish optimal formulations, dosing regimens, and therapeutic outcomes

5. Conclusions

Galantamine has been primarily utilized in the management of Alzheimer’s disease due to its role as a reversible acetylcholinesterase inhibitor. However, alternative delivery routes, such as transdermal and intranasal administration, offer promising non-oral approaches that may reduce systemic side effects and enhance patient adherence. Moreover, these methods hold the potential to broaden the therapeutic applications of galantamine beyond neurodegenerative disorders.

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Despite some preliminary evidence suggesting its potential benefits in the treatment of peripheral nervous system injuries, there is a notable lack of robust, contemporary studies specifically investigating the efficacy and safety of topical galantamine for this patient population. While the theoretical advantages of non-invasive administration, reduced gastrointestinal irritation, and localized drug delivery are compelling, significant challenges persist—most notably, achieving adequate skin permeability and maintaining therapeutic concentrations at the target tissue.

To fully harness the potential of topical galantamine, further rigorous research is required, including the development of advanced transdermal delivery systems capable of optimizing bioavailability and clinical outcomes in neurological and peripheral nerve disorders.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, M.I.; L.P.; D.N..; methodology, M.I..; software, M.I.; P.P; validation, L.P; D.N. and G.B..; formal analysis, M.I., L P..; investigation, M.I..; resources, M.I..; data curation, P.P.; writing—original draft preparation, M.I.; D.N.; P.P; L.P ; writing—review and editing, M.I.; D.N.; E V visualization, P.P.; G.B.; supervision, E.V..; project administration, L.P.; funding acquisition, L.P. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's disease
NHIF	National Health Insurance Fund
SCI	Sciatic nerve injury
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase inhibitors
RA	rheumatoid arthritis

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