Next Nanotechnology 9 (2026) 100515

Contents lists available at ScienceDirect

Next Nanotechnology

journal homepage: www.sciencedirect.com/journal/next-nanotechnology

Review article

Nanotechnology-driven therapeutic strategies for lambert–eaton myasthenic syndrome: Emerging drug delivery and immunomodulatory approaches

Jaghatha Therassama [a], Justus Oliver Jaslin Edward [b], Somasundaram Arumugam [c], Pavazhaviji Pazhani [d], Jose Prakash Dharmian [a,*]

[a] Department of Pharmaceutics, Crescent School of Pharmacy, B.S.Abdur Rahman Crescent Institute of Science & Technology, Chennai, Tamil Nadu 600048, India
[b] Sun College of Pharmacy and Research Centre, Kanyakumari District, Tamil Nadu, 629204, India
[c] National Institute of Pharmaceutical Education and Research (NIPER)-Kolkata, Chunilal Bhawan, 168, Maniktala Main Road, Kolkata, West Bengal 700054, India
[d] Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Sciences, Technology and Advanced Studies, Pallavaram, Chennai, Tamil Nadu 600043, India

ARTICLE INFO

Keywords:
Lambert-Eaton Myasthenic Syndrome
Neuromuscular junction
Voltage-Gated P/Q Calcium Channels
Nanoparticle drug delivery
Blood Nerve Barrier
Nano-immunotherapy

ABSTRACT

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular disorder characterized by impaired acetylcholine release due to autoantibody-mediated targeting of presynaptic P/Q-type voltage-gated calcium channels. Although symptomatic therapies such as amifampridine and immunomodulatory agents provide clinical benefit, their efficacy is limited by short half-life, fluctuating plasma concentrations, systemic toxicity, and dose-dependent adverse effects, including seizures. These limitations highlight the need for advanced drug delivery systems. Recent advances in nanotechnology offer promising strategies to enhance therapeutic precision, bioavailability, and safety in LEMS management. Nanoparticle-based platforms including polymeric nanoparticles and lipid-based nanocarriers enable controlled drug release and improved pharmacokinetic stability, which may help maintain sustained plasma concentrations and thereby enhance drug availability at the neuromuscular junction. In addition, nanocarriers may facilitate improved transport across physiological barriers such as the Blood Nerve Barrier, potentially increasing drug accumulation at presynaptic terminals. Intranasal nanoformulations are explored as a non-invasive systemic delivery strategy, leveraging the highly vascularized nasal mucosa to enhance drug absorption and bypass hepatic first-pass metabolism, thereby improving systemic exposure rather than enabling direct central nervous system targeting. Furthermore, nano-enabled immunomodulation may allow selective suppression of pathogenic autoantibodies while minimizing systemic immunosuppression. This review provides a comprehensive overview of LEMS pathophysiology and current therapies, with a focused discussion on nanotechnology-driven approaches that may overcome existing pharmacological limitations. Future perspectives in targeted delivery, nano-immunotherapy, and biomarker-guided treatment strategies are also highlighted.

1. Introduction

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of the neuromuscular junction characterized by impaired acetylcholine release due to autoantibody-mediated disruption of presynaptic voltage-gated calcium channels. The condition was first described in 1953 by Anderson and colleagues, and later distinguished from myasthenia gravis by Eaton and Lambert based on its unique electrophysiological features. In 1982, Newsom-Davis formally introduced the term LEMS in recognition of Lambert's contributions [1]. Clinically, LEMS is classified into paraneoplastic and non-paraneoplastic forms. The paraneoplastic variant is most commonly associated with small cell lung carcinoma, whereas the non-paraneoplastic form is typically linked to autoimmune mechanisms. Lung Carcinoma, in which tumor-expressed neuronal antigens trigger immune cross-reactivity against presynaptic P/Q-type calcium channels [2]. In contrast, the non-paraneoplastic form occurs independently of malignancy and is often associated with an underlying autoimmune predisposition,

* Corresponding author.
E-mail address: jose88prakash@gmail.com (J.P. Dharmian).

https://doi.org/10.1016/j.nxnano.2026.100515
Received 30 March 2026; Received in revised form 3 May 2026; Accepted 10 May 2026
Available online 20 May 2026

including specific HLA haplotypes such as HLA-B8, DR3, and DQ2 [3]. Circulating antibodies targeting P/Q-type voltage-gated calcium channels are detected in approximately 85–90% of affected individuals [4]. The binding of autoantibodies to presynaptic P/Q-type voltage-gated calcium channels reduces calcium influx during nerve depolarization, leading to impaired acetylcholine release and compromised neuromuscular transmission [5].

Clinically, Lambert–Eaton myasthenic syndrome typically presents with progressive proximal muscle weakness, initially affecting the lower limbs and later involving the shoulder girdle and distal muscles. Bulbar features such as dysarthria and dysphagia may emerge in advanced stages, and ocular involvement can also occur. Autonomic symptoms, including dry mouth and orthostatic intolerance, are common. Disease progression usually occurs over weeks to months, reflecting cumulative impairment of neuromuscular transmission. Major risk factors for paraneoplastic LEMS include long-term tobacco exposure, advanced age, and environmental carcinogens such as radon. The identification of voltage-gated calcium channel antibodies in the 1980s and 1990s significantly improved diagnostic accuracy and advanced understanding of disease mechanisms. Subsequent studies established that antibodies targeting P/Q-type calcium channels are the primary immunological drivers of LEMS [6].

Diagnosis is established using electrophysiological testing, particularly repetitive nerve stimulation, along with serological detection of voltage-gated calcium channel antibodies. Given its rarity and frequent association with early-stage malignancy—especially small cell lung carcinoma—early recognition is essential to enable prompt oncological evaluation. Epidemiological data indicate that LEMS is an uncommon disorder. A large study from the United States Veterans Affairs healthcare system reported a prevalence of approximately 2.6 cases per million and an annual incidence of 0.6 cases per million, findings consistent with reports from European populations [7]. The current gold-standard symptomatic therapy for Lambert–Eaton myasthenic syndrome is Amifampridine (3,4-diaminopyridine), a potassium channel blocker that enhances presynaptic depolarization and facilitates calcium influx. However, its clinical utility is limited by a short elimination half-life (approximately 2 h), resulting in fluctuating plasma concentrations and variable therapeutic response. In addition, dose-dependent adverse effects, particularly an increased risk of seizures at higher doses, further restrict its use [8]. These pharmacokinetic and safety limitations highlight the need for advanced drug delivery strategies capable of providing controlled and sustained drug release. Nanotechnology-based delivery systems offer a promising approach to overcome these limitations by improving pharmacokinetic stability and reducing peak-related toxicity.

The present review critically examines the pathophysiology and current therapeutic approaches for Lambert–Eaton myasthenic syndrome, with particular emphasis on the emerging role of nanomedicine-based drug delivery systems in overcoming existing pharmacological limitations. Conventional treatments primarily aim to enhance synaptic acetylcholine availability or suppress autoimmune activity; however, these approaches do not address the underlying disease mechanisms and are often limited by pharmacokinetic variability, systemic toxicity, and safety concerns. Recent advances in nanotechnology have enabled the development of controlled-release systems, improved bioavailability, and targeted delivery strategies that enhance tissue-specific drug distribution. In neurological and immune-mediated conditions, nanoparticle-based formulations have demonstrated the ability to stabilize plasma drug levels and reduce adverse effects associated with fluctuating exposure. By integrating insights from neurology, immunology, and nanotechnology, this review highlights the translational potential of polymeric and lipid nanocarriers, intranasal nanoformulations, and nano-enabled immunomodulatory approaches as precision-oriented strategies for improving therapeutic outcomes in LEMS.

2. LEMS criteria for diagnosis

Lambert–Eaton myasthenic syndrome is suspected based on characteristic clinical features, including proximal muscle weakness, reduced or absent deep tendon reflexes, and autonomic dysfunction. Definitive diagnosis requires an integrated approach combining clinical assessment, electrophysiological studies, and serological testing. Confirmation is typically achieved through electromyography and repetitive nerve stimulation, supported by the detection of antibodies against presynaptic voltage-gated calcium channels.The disorder is characterized by progressive muscle weakness, fatigue, and autonomic symptoms, with occasional ocular involvement such as diplopia. Proximal lower limb weakness is often the initial manifestation and may impair ambulation. A substantial proportion of cases are associated with small cell lung carcinoma, and neurological symptoms may precede or coincide with tumor detection. Epidemiological data indicate that approximately 50–70% of patients with LEMS have an underlying malignancy, most commonly small cell lung carcinoma.

Laboratory evaluation plays a supportive role in the diagnosis of Lambert–Eaton myasthenic syndrome, with particular emphasis on the serological detection of antibodies directed against voltage-gated calcium channels (VGCCs). Circulating P/Q-type VGCC antibodies are identified in the majority of affected individuals and provide high diagnostic specificity. Although routine investigations such as complete blood count and renal or hepatic function tests may be performed to assess overall clinical status or exclude alternative causes, confirmation of Lambert–Eaton myasthenic syndrome relies primarily on targeted serological assays. These autoantibodies bind to presynaptic calcium channels at the neuromuscular junction, reducing calcium influx and impairing acetylcholine release, thereby underlying the characteristic transmission defect observed in this disorder [9–13].

Imaging studies are not used for the direct diagnosis of Lambert–Eaton myasthenic syndrome, as the disorder primarily affects the neuromuscular junction rather than the central nervous system. Instead, radiological investigations such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) are performed to screen for underlying malignancies, particularly small cell lung carcinoma in suspected paraneoplastic cases. Electrophysiological testing remains fundamental for diagnostic confirmation. Nerve conduction studies typically show reduced resting compound muscle action potential (CMAP) amplitudes, reflecting impaired presynaptic acetylcholine release. Repetitive nerve stimulation demonstrates a characteristic incremental response following high-frequency stimulation or brief voluntary contraction, distinguishing LEMS from myasthenia gravis, which more commonly exhibits a decremental pattern. Single-fiber electromyography may reveal increased jitter and transmission instability, further supporting a presynaptic defect. Electrodiagnostic abnormalities are often detectable early in the disease course, particularly in proximal limb muscles, and are commonly assessed using the ulnar or median nerves. The integration of electrophysiological findings with serological detection of P/Q-type voltage-gated calcium channel antibodies enables high-specificity diagnosis [14–17].

The diagnostic algorithm and principal investigative modalities used in suspected cases of Lambert–Eaton myasthenic syndrome are summarized in Fig. 1, illustrating the integrated roles of clinical evaluation, electrophysiological testing, and serological analysis. Among these, electrodiagnostic assessment remains the primary confirmatory approach. A key diagnostic feature is a marked incremental increase in compound muscle action potential amplitude following high-frequency repetitive nerve stimulation or brief voluntary contraction. This facilitation response reflects impaired presynaptic calcium-dependent neurotransmitter release. In patients with suspected LEMS, repetitive nerve stimulation and post-exercise testing should be performed by an experienced neurologist or neurophysiologist to confirm the presence of a presynaptic transmission defect [18–24].

Repetitive nerve stimulation (RNS) is a key electrophysiological tool

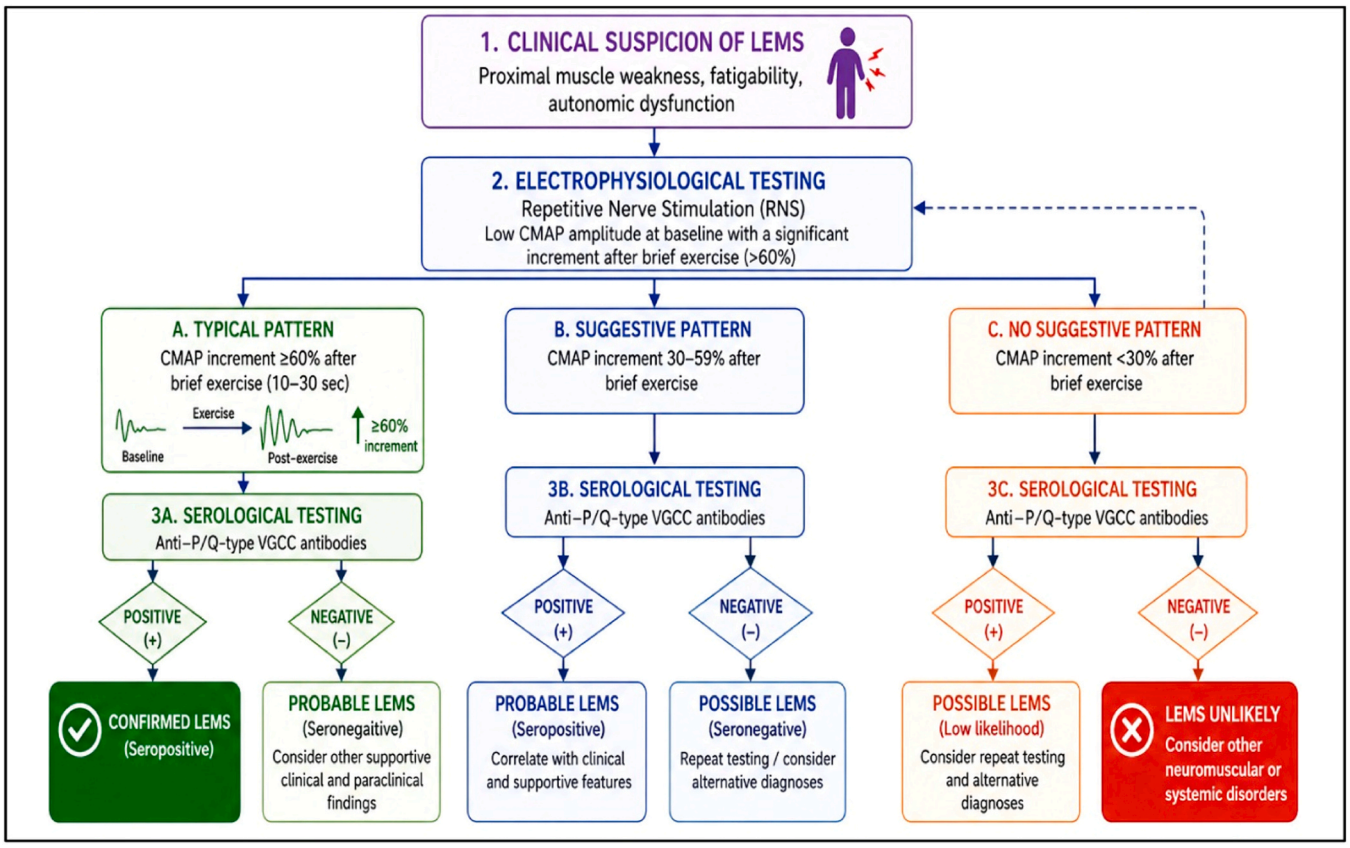

Fig. 1. Overview of key diagnostic modalities used in the evaluation of suspected LEMS.

in the evaluation of Lambert–Eaton myasthenic syndrome. At baseline, motor nerve conduction studies typically demonstrate reduced compound muscle action potential (CMAP) amplitudes, often less than 50% of the expected normal value, reflecting impaired presynaptic acetylcholine release. Low-frequency stimulation may produce a modest decremental response; however, the defining feature of LEMS is a marked incremental increase in CMAP amplitude following high-frequency stimulation or brief voluntary contraction. This post-activation facilitation results from transient calcium accumulation within the presynaptic terminal, partially restoring neurotransmitter release. A reduction in resting CMAP amplitude exceeding 10% of expected values is considered abnormal and is observed in a substantial proportion of affected individuals, supporting the diagnosis of a presynaptic neuromuscular transmission defect [3,25–29].

The post-exercise test is an important electrophysiological adjunct in the evaluation of Lambert–Eaton myasthenic syndrome. Following brief maximal voluntary contraction, a substantial increase in compound muscle action potential (CMAP) amplitude is typically observed in approximately 80–95% of affected individuals. This facilitation reflects a transient increase in presynaptic calcium availability, temporarily enhancing acetylcholine release. It is essential to distinguish true post-exercise facilitation from pseudo-facilitation, which may result from technical factors such as unintended muscle contraction or electrode displacement during testing. Careful technique and accurate interpretation are therefore required. In addition, routine nerve conduction studies often demonstrate reduced resting CMAP amplitudes, consistent with impaired presynaptic neurotransmission in LEMS [10,30–33].

In summary, the diagnosis of Lambert–Eaton myasthenic syndrome requires a comprehensive and integrated approach that combines clinical assessment, electrophysiological evaluation, serological testing, and appropriate malignancy screening. Characteristic findings include reduced resting compound muscle action potential (CMAP) amplitudes with post-activation facilitation, along with the detection of P/Q-type voltage-gated calcium channel antibodies, which together establish the diagnosis with high specificity. Early recognition is particularly important due to the strong association with small cell lung carcinoma, as timely oncological evaluation can significantly influence prognosis and management. Accurate diagnostic stratification not only guides therapeutic decisions but also provides a foundation for emerging precision-based approaches, including nanomedicine-driven strategies aimed at improving targeted treatment outcomes.

3. Neuropathology of LEMS

Normal neuromuscular transmission depends on the regulated release of acetylcholine from the presynaptic motor nerve terminal. Upon arrival of an action potential, voltage-gated calcium channels open, allowing calcium influx into the nerve terminal. The resulting increase in intracellular calcium triggers synaptic vesicle fusion and acetylcholine release into the synaptic cleft. Acetylcholine then binds to nicotinic receptors on the postsynaptic motor endplate, leading to membrane depolarization and subsequent muscle contraction through calcium release from the sarcoplasmic reticulum [10]. In Lambert–Eaton myasthenic syndrome (LEMS), circulating IgG autoantibodies selectively target presynaptic P/Q-type voltage-gated calcium channels (VGCCs) localized at the active zones of the motor nerve terminal. These active zones are specialized regions responsible for calcium-dependent synaptic vesicle docking, fusion, and neurotransmitter release. Antibody binding leads to a reduction in functional channel density and disrupts calcium influx during nerve depolarization. As a result, the intracellular calcium concentration fails to reach the threshold required for efficient synaptic vesicle fusion, leading to a reduction in the quantal release of acetylcholine into the synaptic cleft. This decrease in endplate potential amplitude directly impairs skeletal muscle contraction,

leading to the characteristic muscle weakness observed in LEMS. Fig. 2 schematically illustrates the neuromuscular junction and highlights the disruption of presynaptic calcium channel function underlying the pathophysiology of Lambert–Eaton myasthenic syndrome.

3.1. Non-Paraneoplastic Phenomenon (A-LEMS) & Paraneoplastic Phenomenon (P-LEMS)

LEMS can be broadly classified into autoimmune (A-LEMS) and paraneoplastic (P-LEMS) subtypes based on its underlying etiology. Autoimmune LEMS (A-LEMS) occurs in the absence of an associated malignancy and is primarily driven by an idiopathic immune response directed against presynaptic calcium channels. It is often associated with other autoimmune disorders, reflecting a broader dysregulation of immune tolerance. In contrast, paraneoplastic LEMS (P-LEMS) is most commonly associated with small cell lung carcinoma (SCLC), where tumor cells aberrantly express neuronal antigens similar to presynaptic VGCCs. This antigenic mimicry triggers an immune response that leads to the production of cross-reactive antibodies targeting both tumor cells and neuronal calcium channels. As a result, neurological symptoms may precede the clinical detection of the underlying malignancy. Although both subtypes share a common immunological target, they differ in their clinical progression, prognosis, and therapeutic management, particularly in relation to cancer screening and immunotherapy [34,35]. The distinct immunopathogenic pathways underlying A-LEMS and P-LEMS are illustrated in Figs. 3a and 3b, highlighting differences in antibody induction and their effects on calcium channel function.

(b) Paraneoplastic LEMS: Tumor-induced immune responses generate cross-reactive antibodies against presynaptic calcium channels, leading to impaired neuromuscular transmission.

The neuropathogenesis of autoimmune Lambert–Eaton myasthenic syndrome (A-LEMS) is characterized by antibody-mediated blockade and dysfunction of presynaptic voltage-gated calcium channels, with most antibodies directed against the α1 subunit. This results in reduced calcium influx, leading to impaired acetylcholine release and consequent neuromuscular and autonomic dysfunction. T-cell–mediated immune regulation may modulate disease progression by either promoting or limiting the autoimmune response. Genetic susceptibility also contributes to disease development, as observed in many autoimmune disorders. In non-paraneoplastic LEMS, associations with specific human leukocyte antigen (HLA) haplotypes, including HLA-B8 and HLA-DR3, support the role of inherited immune predisposition. In contrast, paraneoplastic LEMS does not exhibit a consistent HLA association and is not typically linked to genetic susceptibility patterns seen in primary autoimmune conditions. Instead, immune activation in paraneoplastic LEMS is primarily driven by tumor-associated antigen expression. Notably, tumor samples from patients with small cell lung carcinoma and concurrent LEMS have demonstrated altered or reduced expression of HLA class I molecules compared with tumors from patients without neurological involvement. This suggests that differences in tumor–immune interactions may influence the generation of pathogenic antibodies [36–38].

In approximately half of patients with paraneoplastic Lambert–Eaton myasthenic syndrome, small cell lung carcinoma cells aberrantly express antigens related to voltage-gated calcium channels on their surface. This ectopic expression acts as a tumor-associated trigger, promoting the production of autoantibodies that cross-react with presynaptic P/Q-type calcium channels at the neuromuscular junction. The resulting reduction in functional channel density limits calcium influx during depolarization, impairing synaptic vesicle fusion and decreasing acetylcholine release with each action potential. In contrast, individuals with non-paraneoplastic LEMS do not have an underlying malignancy, and the autoimmune response develops independently of tumor-associated antigen expression [39,40].

3.2. Antibodies

Autoantibodies against P/Q-type voltage-gated calcium channels are

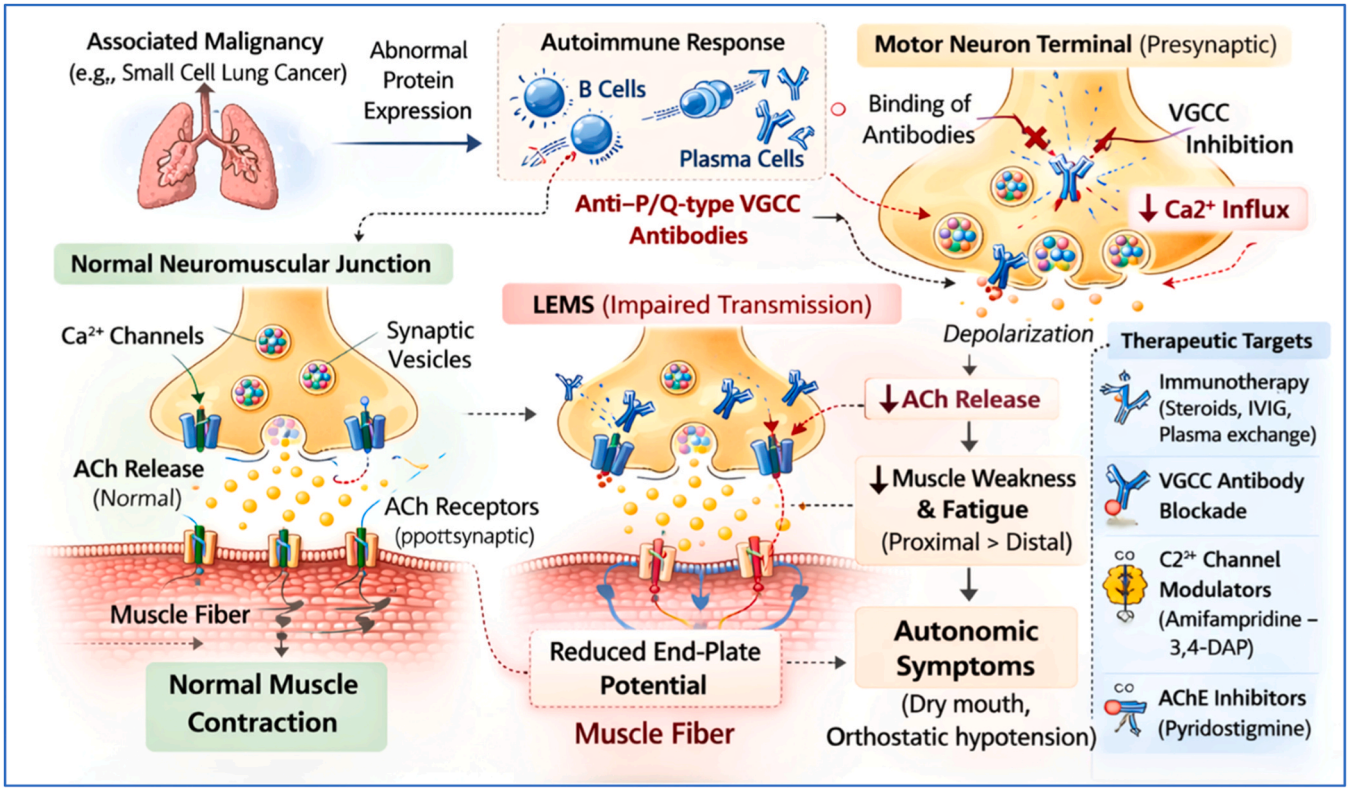

Fig. 2. Pathophysiology of the Neuromuscular Junction in Lambert–Eaton Myasthenic Syndrome.

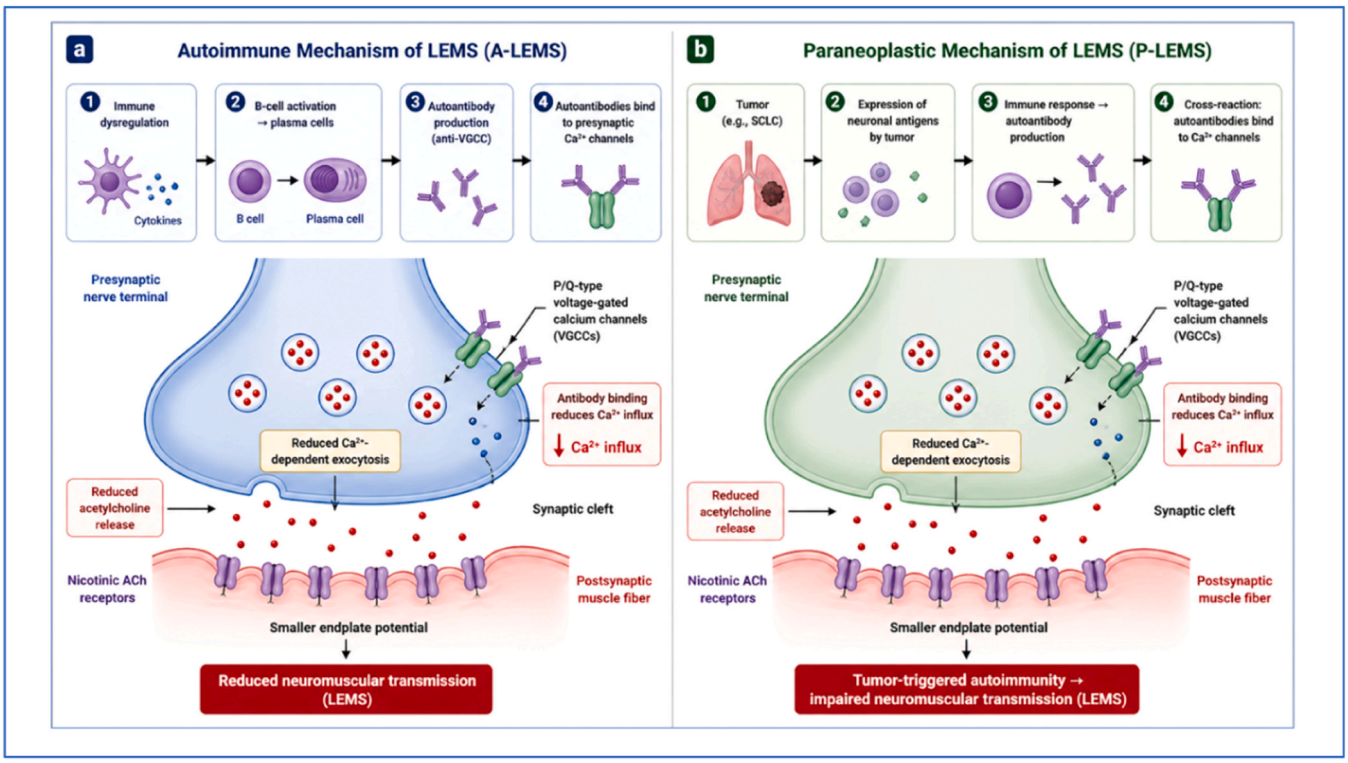

Fig. 3. a) Autoimmune LEMS: B-cell–mediated autoantibodies target presynaptic P/Q-type voltage-gated calcium channels, reducing calcium influx and acetylcholine release.

the principal serological hallmark of Lambert–Eaton myasthenic syndrome and are detected in most affected individuals. These antibodies play a central role in disease pathophysiology by reducing presynaptic calcium influx and impairing acetylcholine release.In paraneoplastic cases, particularly those associated with small cell lung carcinoma, additional tumor-related antibodies may be present. Among these, SOX1 antibodies serve as a useful marker for small cell lung carcinoma and are more frequently observed in paraneoplastic LEMS than in non-paraneoplastic forms.In addition to P/Q-type VGCC antibodies, immune responses against other presynaptic proteins have been reported, including synaptotagmin and muscarinic acetylcholine receptors, which may further affect neurotransmitter release and autonomic function [13, 41]. A subset of patients remains seronegative using conventional assays. In such cases, symptoms may result from low-titer VGCC antibodies below detection thresholds or from antibodies targeting alternative presynaptic antigens. These observations highlight the immunological heterogeneity of Lambert–Eaton myasthenic syndrome and the need for comprehensive serological evaluation in clinically suspected cases.

4. Clinical Profile and Risk Factors

Lambert–Eaton myasthenic syndrome (LEMS) is a disorder of impaired neuromuscular transmission characterized by a combination of motor and autonomic dysfunction. The most consistent clinical feature is progressive, symmetrical proximal muscle weakness, particularly affecting the lower limbs, leading to difficulty in activities such as rising from a seated position, climbing stairs, or walking. A distinctive feature is the transient improvement in muscle strength following brief exertion, known as post-activation facilitation. Autonomic symptoms are common and may include dry mouth, gastrointestinal disturbances, reduced sweating, and sexual dysfunction. Tendon reflexes are typically reduced or absent at rest but may temporarily improve after repeated muscle activation. Bulbar involvement, such as dysarthria or dysphagia, may occur but is usually less prominent than in other neuromuscular junction disorders. Disease occurrence and progression vary by subtype. Paraneoplastic LEMS is strongly associated with malignancy, most commonly small cell lung carcinoma, and is more frequently seen in older individuals with a history of tobacco exposure. In contrast, non-paraneoplastic LEMS is associated with autoimmune predisposition and may coexist with other immune-mediated conditions, with genetic factors such as specific HLA profiles contributing to susceptibility. Clinical progression also differs between subtypes: autoimmune LEMS generally follows a gradual course, whereas paraneoplastic LEMS often progresses more rapidly and may precede tumor detection. Early recognition of these patterns is essential for timely diagnosis, appropriate management, and prompt malignancy screening. The major risk factors associated with LEMS are illustrated in Fig. 4 [42].

4.1. *Pathophysiology and Etiology*

Lambert–Eaton myasthenic syndrome (LEMS) is a neuromuscular disorder caused by immune-mediated disruption of presynaptic voltage-gated calcium channels at the neuromuscular junction. This reduces calcium influx during nerve depolarization, leading to decreased acetylcholine release and impaired neuromuscular transmission. The etiology differs between autoimmune and paraneoplastic form, although both share a common pathogenic mechanism. Autoimmune LEMS (A-LEMS) occurs independently of malignancy and is associated with immune dysregulation and genetic susceptibility, including specific human leukocyte antigen (HLA) haplotypes, which promote the production of autoantibodies against presynaptic calcium channels. In contrast, paraneoplastic LEMS (P-LEMS) is most commonly linked to small cell lung carcinoma, where tumor cells aberrantly express neuronal antigens that trigger an immune response and generate cross-reactive antibodies targeting both tumor tissue and presynaptic calcium channels. Neurological symptoms may therefore precede tumor detection. Despite these differences, both forms converge on a shared functional deficit

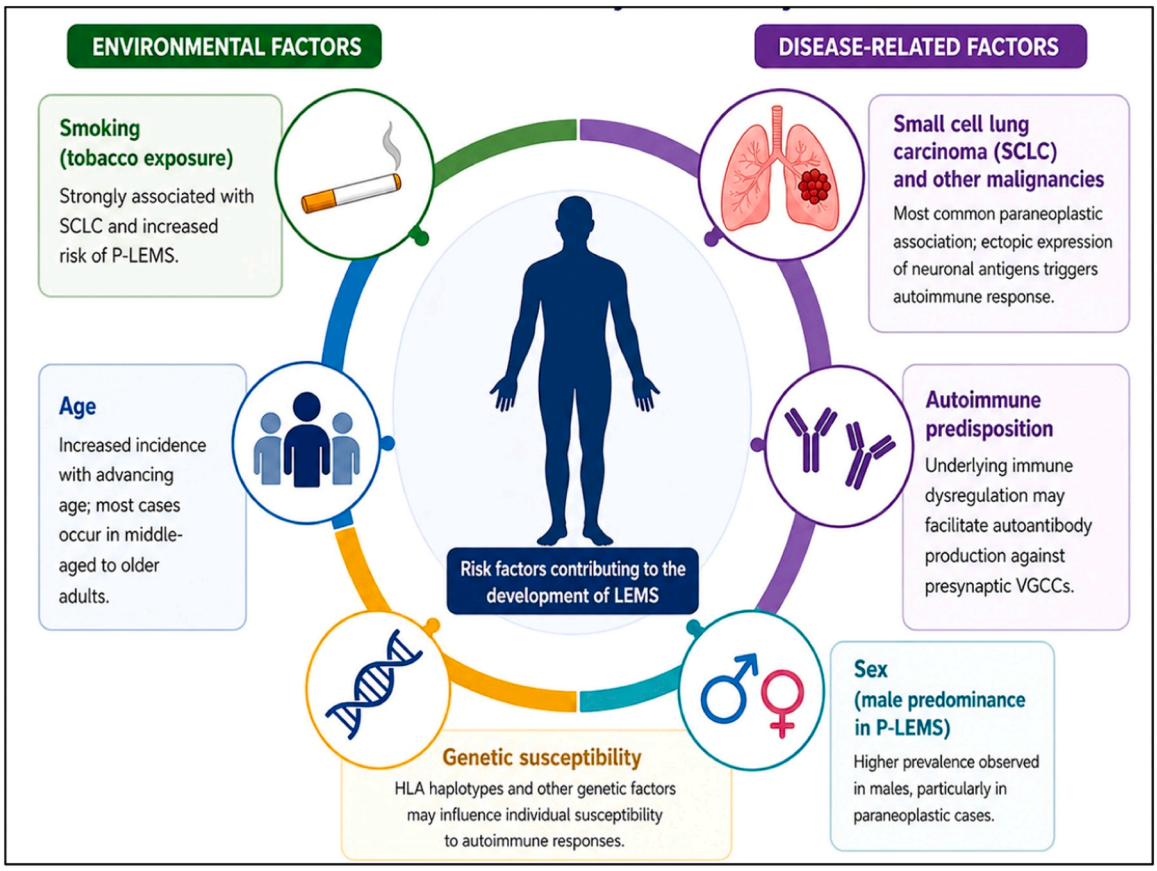

Fig. 4. Major Risk Factors Associated with the Development of Lambert–Eaton Myasthenic Syndrome.

characterized by reduced calcium-dependent acetylcholine release at the neuromuscular junction, which underlies the clinical manifestations of LEMS [39,42–44].

5. Therapeutic Approaches of LEMS

Lambert–Eaton myasthenic syndrome is a rare autoimmune disorder, with an estimated annual incidence of approximately 0.5 cases per million individuals. Management focuses on symptomatic improvement, modulation of the immune response, and treatment of any associated malignancy. Although a definitive cure is not currently available, several pharmacological and immunotherapeutic interventions can significantly improve neuromuscular function and quality of life.Common therapeutic agents include 3,4-diaminopyridine (3,4-DAP), pyridostigmine, guanidine, corticosteroids, intravenous immunoglobulin (IVIg), plasmapheresis, and rituximab [39,45–48].

Symptomatic management of Lambert–Eaton myasthenic syndrome focuses on agents that enhance presynaptic acetylcholine release at the neuromuscular junction. Amifampridine (3,4-diaminopyridine) is the first-line symptomatic treatment for Lambert–Eaton myasthenic syndrome, acting as a potassium channel blocker that prolongs presynaptic depolarization and enhances calcium influx. Despite its clinical efficacy, its therapeutic use is limited by a short elimination half-life (approximately 2 h), which leads to fluctuating plasma concentrations and variable symptom control. In addition, dose-dependent adverse effects, particularly an increased risk of seizures at higher doses (typically exceeding 60–80 mg/day), restrict its safe use. These limitations highlight the need for advanced drug delivery strategies capable of providing sustained release and minimizing peak-related toxicity. In 2019, regulatory approval in the United States expanded access to amifampridine formulations for pediatric and adult populations. Amifampridine phosphate is approved for the treatment of LEMS in adults, while pediatric approval has been granted for specific age groups under defined clinical indications. These developments have improved therapeutic accessibility and standardized management of symptomatic LEMS. [49–51].

5.1. Immunomodulatory therapy

Immunomodulatory therapy in Lambert–Eaton myasthenic syndrome aims to reduce autoantibody production and limit immune-mediated damage to presynaptic calcium channels. These interventions are particularly indicated in patients with significant functional impairment or progressive disease. Commonly used treatments include intravenous immunoglobulin (IVIg), corticosteroids, steroid-sparing immunosuppressants such as azathioprine and cyclosporine, plasma exchange (PLEX), and the monoclonal antibody rituximab. IVIg exerts immunomodulatory effects through multiple mechanisms, including modulation of Fc receptor activity, neutralization of pathogenic antibodies, and alteration of cytokine signaling. In LEMS, IVIg may transiently reduce circulating autoantibody activity and improve neuromuscular transmission, resulting in short-term improvement in muscle strength. Although generally well tolerated, IVIg may be associated with adverse effects such as headache, fever, and infusion-related reactions [37,45–47].

Corticosteroids, such as prednisone, suppress immune activation and reduce autoantibody production, thereby improving neuromuscular function in selected patients. Due to the risk of long-term adverse effects, steroid-sparing agents are often introduced to maintain sustained immunosuppression [46,48,49]. Azathioprine interferes with lymphocyte proliferation and is commonly used as a long-term immunosuppressive agent in LEMS. Cyclosporine, another immunosuppressant, inhibits T-cell activation and may be considered in patients who are refractory to first-line therapies. However, their use is limited by delayed onset of action and potential adverse effects, necessitating

careful monitoring and individualized treatment strategies [42,52,53].

A summary of the principal pharmacologic agents, their mechanisms, dosage regimens, and clinical applications used in the management of LEMS is provided in Table 1.

5.2. Oncological Management in Paraneoplastic LEMS

In paraneoplastic Lambert–Eaton myasthenic syndrome, oncological management plays a central role in disease control. Reduction of tumor burden, particularly in small cell lung carcinoma, decreases the expression of neuronal antigens responsible for triggering the autoimmune response, thereby leading to a gradual decline in circulating P/Q-type voltage-gated calcium channel autoantibodies, as summarized in Table 1. This reduction in autoantibody levels contributes to partial restoration of neuromuscular transmission. However, the clinical benefits of tumor-directed therapies such as chemotherapy or radiotherapy are often delayed, and symptomatic improvement may not occur immediately. This temporal gap between initiation of cancer treatment and reduction in autoantibody titers can significantly affect patient quality of life, as highlighted in Table 1.

In this context, adjunctive therapeutic strategies, including nanotechnology-based drug delivery and targeted immunomodulation, may help bridge this gap by providing more rapid and sustained symptom control while underlying oncological therapy takes effect. Furthermore, biomarkers such as SOX1 antibodies may serve as useful indicators of treatment response, and their monitoring could provide a complementary approach for evaluating the effectiveness of oncological and immunomodulatory interventions.

5.3. Supportive and Physical Rehabilitation Strategies

Balance and coordination training are particularly important, as impaired neuromuscular transmission may lead to instability and an increased risk of falls. Gait disturbances are common, and rehabilitation strategies may include gait retraining, postural correction, and, when necessary, the use of assistive devices such as canes, walkers, or orthotic supports to facilitate safe ambulation. Fatigue management is also a key component of supportive care. Rehabilitation protocols can leverage the physiological “warm-up” effect characteristic of LEMS, in which brief isometric or repetitive muscle contractions transiently enhance acetylcholine release at the neuromuscular junction, thereby facilitating improved muscle activation and enabling more effective training sessions. Energy conservation strategies, including structured activity pacing, scheduled rest periods, and ergonomic optimization, can help reduce exertional fatigue. Additional lifestyle measures—such as moderate exercise within tolerance, adequate rest, stress management, and appropriate nutritional support—further contribute to symptom control and functional independence [56].

While oncological interventions and physical rehabilitation strategies address the broader clinical and functional aspects of Lambert–Eaton myasthenic syndrome, they do not directly resolve the underlying presynaptic instability at the neuromuscular junction. Current therapeutic approaches largely remain reactive, focusing on symptom management rather than precise modulation of disease mechanisms. In this context, emerging nanotechnology-based strategies offer a paradigm shift toward precision-oriented neurology. Advanced platforms, including targeted nanocarriers and nano-enabled biosensing systems, provide the potential to enhance drug localization, stabilize synaptic transmission, and enable real-time monitoring at the molecular level. The following sections explore how these innovations may overcome existing therapeutic limitations and improve disease management in LEMS.

6. Limitations of Conventional Pharmacotherapy in LEMS

Amifampridine remains the principal symptomatic therapy for LEMS, acting through inhibition of presynaptic voltage-gated potassium channels to prolong depolarization and facilitate calcium-dependent acetylcholine release. However, its relatively short elimination half-life (approximately 2 h) contributes to pharmacokinetic (PK) instability, characterized by a high peak-to-trough (C_{max}/C_{min}) ratio. This results in fluctuating plasma drug levels, leading to variable clinical response and an increased risk of peak-related adverse effects, including seizures and paresthesia. Pyridostigmine, an acetylcholinesterase inhibitor, enhances the availability of acetylcholine at the neuromuscular junction by inhibiting its enzymatic breakdown. However, its efficacy is inherently limited in LEMS, as its mechanism depends on the presence of acetylcholine in the synaptic cleft. Given that LEMS is characterized by reduced quantal acetylcholine release, pyridostigmine has limited substrate to act upon, which explains its modest benefit and poor effectiveness as monotherapy [57]. Immunomodulatory therapies, including corticosteroids, azathioprine, intravenous immunoglobulin, and rituximab, may benefit selected patients; however, these agents have broad systemic effects and are associated with risks such as infection,

Table 1
Pharmacological therapies currently used in the management of LEMS, including symptomatic and immunomodulatory treatment strategies.

Drug / Agent	Mechanism of Action	Dosage Regimen	Clinical Applications	References
Symptomatic Treatment				
Amifampridine (3,4-DAP)	Blocks voltage-gated potassium channels, prolonging presynaptic depolarization and enhancing calcium influx and acetylcholine release at the neuromuscular junction	15–30 mg/day in divided doses (3–4 times daily); maximum dose generally not exceeding 80 mg/day	Recommended first-line symptomatic therapy for LEMS	[46,48,49]
Pyridostigmine	Acetylcholinesterase inhibitor that increases acetylcholine availability at the neuromuscular junction	Approximately 30 mg three times daily	May be combined with guanidine	[50]
Guanidine	Inhibits voltage-gated potassium channels and enhances acetylcholine release	Usually less than 1000 mg/day when used with pyridostigmine	Rarely used due to toxicity	[51]
Immunomodulatory Therapy				
Intravenous Immunoglobulin (IVIg)	Provides nonspecific immunomodulatory effects by neutralizing circulating autoantibodies	1 g/kg/day for 2 consecutive days	Clinical benefit may persist for several weeks	[42,52]
Prednisolone / Prednisone	Corticosteroid that suppresses immune activity and reduces autoantibody production	Prednisone 1 mg/kg/day or 1.5 mg/kg on alternate days; often combined with azathioprine (2.5 mg/kg/day) or cyclosporine (3–4 mg/kg/day)	Used when symptomatic therapy is insufficient	[53]
Azathioprine / cyclosporine	By reducing the activity of immune cells, azathioprine can help to suppress the autoimmune response and alleviate LEMS symptoms			[46,51–54]
Plasmapheresis (PLEX)	Plasma exchange removes circulating pathogenic autoantibodies	Typically, 3–4 L plasma removed per exchange; 5–15 sessions over 5–19 days	Used in severe cases or LEMS crisis	[45,51]
Rituximab	Anti-CD20 monoclonal antibody that depletes B-cells producing pathogenic antibodies	375 mg/m² weekly for 4 weeks, followed by maintenance dosing if required	Considered in refractory disease or when IVIg/PLEX are not tolerated	[39,55]

long-term toxicity, and generalized immunosuppression. In addition, current treatments do not selectively target autoreactive immune cells at the primary site of disease. These limitations highlight the need for innovative delivery strategies that can maintain stable drug exposure, reduce systemic toxicity, and enable more precise immune modulation.

7. Nanotechnology-Based Drug Delivery Strategies in LEMS

Nanotechnology offers a versatile platform for improving therapeutic delivery through nanoscale carriers, typically ranging from 10 to 200 nm in size. A summary of nanocarrier systems, their proposed mechanisms in LEMS, and available preclinical evidence is provided in Table 2. Nanocarrier targeting strategies at the neuromuscular junction including presynaptic targeting, BNB penetration, immunomodulation, and stimuli-responsive delivery are illustrated in Fig. 5.

An important consideration in nanotechnology-based drug delivery for autoimmune disorders such as LEMS is the potential immunogenicity of the carrier system itself. Certain nanomaterials may interact with immune cells and, depending on their composition, size, and surface characteristics, could potentially induce immune activation or function as adjuvant-like agents [58]. Such effects may theoretically exacerbate underlying autoimmune responses if not carefully controlled. Therefore, the selection of biocompatible and biodegradable materials is critical in minimizing unintended immunostimulation. Surface modification strategies, including PEGylation, can reduce opsonization and immune recognition, thereby improving biocompatibility and circulation time. In addition, careful optimization of nanoparticle physicochemical properties and rigorous preclinical evaluation are essential to ensure immunological safety while maintaining therapeutic efficacy. Polymeric nanoparticles composed of biodegradable materials such as poly (lactic-co-glycolic acid), chitosan, and polyethylene glycol derivatives have shown significant potential for controlled drug delivery [59]. Encapsulation of amifampridine within polymeric matrices may attenuate rapid systemic peak concentrations while maintaining sustained therapeutic levels over extended periods. An important consideration in the development of controlled-release nanoformulations is the potential risk of dose dumping resulting from nanocarrier instability. Sudden release of encapsulated amifampridine may result in transient increases in systemic drug levels, thereby elevating the risk of dose-dependent adverse effects, including seizures, as discussed in earlier sections. Given the narrow therapeutic window of amifampridine, formulation parameters such as polymer integrity, nanoparticle stability, and release kinetics must be carefully optimized to ensure predictable and sustained drug delivery. Strategies including cross-linking stabilization, surface coating, and rigorous in vitro and in vivo release profiling are essential to minimize unintended rapid drug release [60]

Beyond conventional controlled-release systems, stimuli-responsive nanocarriers represent an emerging strategy for enhancing therapeutic precision. These systems can be engineered to respond to physiological or biochemical triggers, such as pH changes or enzymatic activity, enabling site-specific and time-dependent drug release. In the context of LEMS, such platforms could theoretically synchronize amifampridine release with periods of increased synaptic demand, offering a bio-synchronized approach to neuromuscular modulation. Surface

Table 2
Nanoparticle-based drug delivery platforms explored for targeted therapy and neuromuscular modulation in Lambert–Eaton Myasthenic Syndrome.

Nanoparticle System	Drug Delivery Strategy	Mechanism in LEMS (NMJ-specific)	Preclinical Evidence	Proposed Mechanism in LEMS	Key Advantages	References
Polymeric Nanoparticles (PLGA, Chitosan)	Enable sustained and controlled release of encapsulated therapeutic agents through surface-modified carriers	Maintains stable amifampridine levels, stabilises presynaptic Ca^{2+} influx, and improves ACh release	Preclinical studies show enhanced neuronal uptake and membrane interaction	Long-acting delivery of symptomatic drugs, such as potassium channel modulators, is used in LEMS management	Improved pharmacokinetic stability and reduced frequency of drug administration	[65–69]
Lipid Nanoparticles	Encapsulate therapeutic molecules within lipid structures that facilitate efficient cellular uptake	Facilitates fusion with presynaptic membranes enhances drug retention at NMJ.	Evaluated in neurodrug delivery models for controlled release	Delivery of immunomodulatory drugs to regulate autoimmune activity associated with LEMS.	Excellent biocompatibility and enhanced bioavailability of therapeutic compounds	[70–74]
Solid Lipid Nanoparticles (SLNs)	Lipid-based matrix systems protect drugs and permit gradual drug release into systemic circulation	Sustained drug availability at presynaptic terminals supports continuous neurotransmission	Demonstrated in autoimmune disease models for immune cell targeting	Sustained delivery of neuroactive agents affecting neuromuscular transmission	Improved stability of encapsulated drugs and prolonged therapeutic activity	[75–78]
Dendrimers	Highly branched nanocarriers capable of transporting multiple drug molecules to targeted sites	Target immune cells (B cells) reduce autoantibody production against VGCCs	Preclinical studies show magnetically guided targeted delivery	Targeted modulation of immune cells involved in autoantibody production	High drug-loading capacity and potential for site-specific targeting	[79]
Magnetic Nanoparticles	Drug-loaded nanocarriers guided by external magnetic fields toward target tissues	Enhances localized drug accumulation near neuromuscular regions	Used in biosensing and targeted delivery experimental studies	Precise delivery of therapeutic agents to neuromuscular regions	Potential for combined imaging and therapeutic delivery (theragnostic)	[80,81]
Gold Nanoparticles	Surface-functionalized nanoparticles enabling targeted drug delivery and diagnostic imaging	Enable ligand-based targeting and potential biosensing of VGCC antibodies	Neuronal targeting validated in experimental neurodelivery systems	Potential theragnostic applications for monitoring neuromuscular disease progression	High surface area allowing attachment of ligands or therapeutic molecules	[82]
Intranasal Nanoparticle Systems	Facilitate direct transport of therapeutic agents through the nasal route toward neural tissues	Improves systemic bioavailability and maintains consistent drug levels at NMJ	Preclinical nasal delivery models demonstrate improved systemic absorption	Rapid delivery of neuroactive drugs influencing neuromuscular signalling pathways	Non-invasive administration and enhanced drug availability in neural tissues	[83,84]
Stimuli-Responsive Nanocarriers	Triggered release (pH, enzyme, activity dependent)	Synchronizes drug release with synaptic activity, supports dynamic ACh release	Early-stage experimental models demonstrate stimulus-triggered release	Precision neuromodulation therapy	Reduced off-target effects; controlled release timing	[85,86]

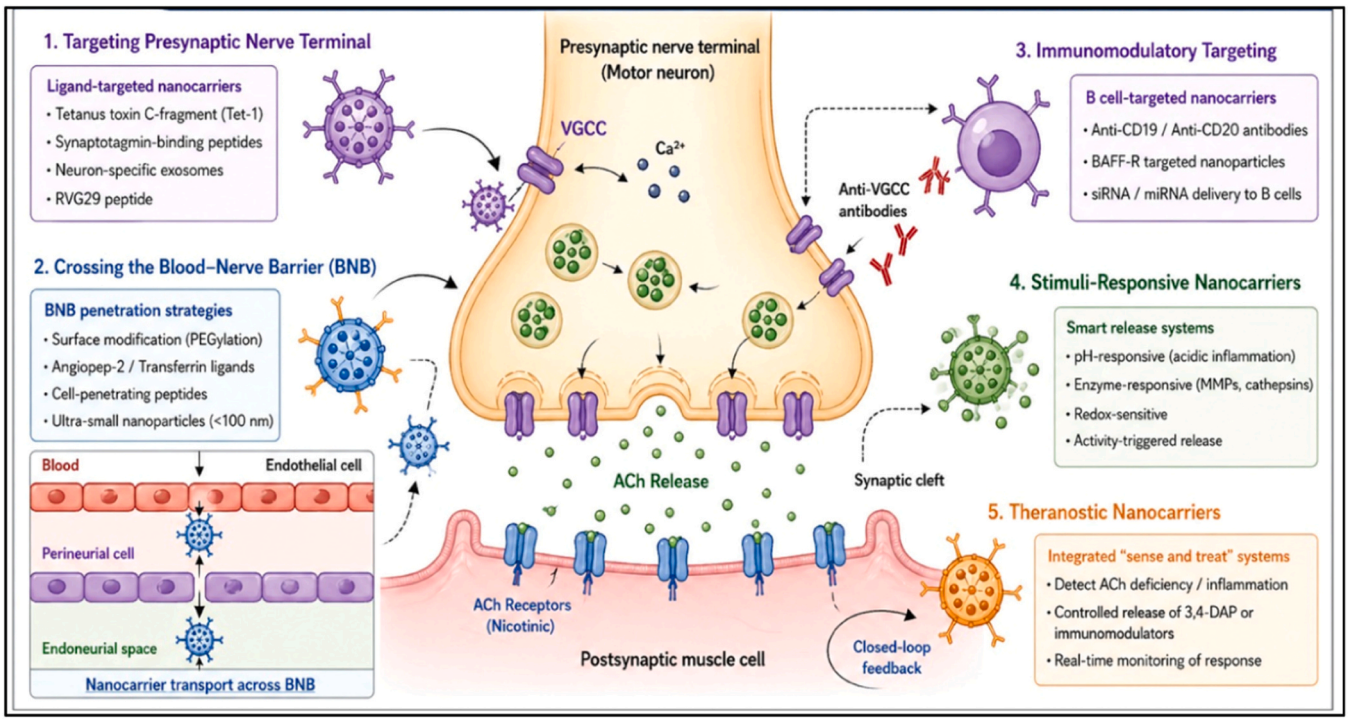

Fig. 5. Schematic of nano carrier targeting strategies at the neuromuscular junction in LEMS.

functionalization of nanocarriers represents a key strategy for enhancing delivery precision. Emerging approaches include the use of neuronal-binding ligands such as tetanus toxin C-fragment (TTC), Tet-1 peptide, and nucleic acid-based aptamers, which can facilitate selective interaction with neuronal membranes and promote accumulation at peripheral nerve terminals. Although these ligands do not directly bind presynaptic P/Q-type voltage-gated calcium channels, they may enhance synaptic localization and improve therapeutic targeting efficiency. Such ligand-conjugated nanocarriers offer a promising avenue for achieving more refined delivery to neuromuscular junction components.However, direct ligand-mediated targeting of presynaptic P/Q-type voltage-gated calcium channels remains a significant challenge due to their limited extracellular accessibility and structural complexity. At present, no clinically validated surface ligands have been established for the selective targeting of CaV2.1 channels. Emerging experimental approaches, including neuronal-binding peptides such as tetanus toxin C-fragment and Tet-1 peptide, synaptic vesicle-associated protein ligands, and neuron-specific aptamers, have demonstrated potential for enhancing neuronal targeting and synaptic localization, although they do not directly bind presynaptic calcium channels [60,61].

In the absence of highly specific targeting ligands, nanocarrier systems rely predominantly on indirect delivery mechanisms. These include prolonged systemic circulation, improved pharmacokinetic stability, and optimized particle size (typically 100–200 nm), which collectively enhance drug diffusion across the blood–nerve barrier. Surface modifications such as PEGylation may reduce immune clearance and improve permeability, while lipid-based nanocarriers may facilitate transcellular transport. In addition, nanoparticle systems may exploit neuronal uptake and axonal transport mechanisms to further enhance delivery efficiency [62]. Disease-associated microenvironmental changes, including immune-mediated alterations in vascular permeability, may also support nanoparticle access to peripheral nerve terminals. Furthermore, physicochemical optimization of nanocarriers, including size and surface engineering, contributes to improved transport across biological barriers such as the blood–nerve barrier [63].

The blood–nerve barrier (BNB) represents a major limitation in achieving effective drug concentrations at the NMJ. Nanocarriers designed within an optimal size range (approximately 100–200 nm) can enhance transport across the BNB via transcellular and adsorptive-mediated pathways. [64]. Surface modification strategies such as PEGylation improve circulation time, reduce opsonization, and facilitate endothelial uptake. Lipid-based nanocarriers further enhance transcellular transport by interacting with cellular membranes, while disease-associated alterations in vascular permeability may promote nanoparticle accumulation in affected nerve regions. These mechanisms recollectively improve drug delivery efficiency to presynaptic terminals without requiring excessively high systemic concentrations [64]

Lipid-based nanocarriers, including liposomes and solid lipid nanoparticles, provide high biocompatibility and efficient encapsulation of both hydrophilic and lipophilic agents. These systems enhance pharmacokinetic stability and reduce toxicity through sustained release. Incorporation of symptomatic or immunomodulatory agents into lipid nanoparticles may minimize plasma fluctuations and lower the risk of adverse neurological effects associated with conventional dosing.

Intranasal nano-delivery represents an additional innovative strategy with significant translational potential. In the context of LEMS, this route is primarily utilized to enhance systemic bioavailability through the highly vascularized nasal mucosa, rather than for direct nose-to-brain delivery. Nanoformulations administered via the intranasal route bypass hepatic first-pass metabolism and facilitate rapid systemic absorption, thereby improving pharmacokinetic consistency. Mucoadhesive nanoparticles, particularly those based on chitosan, enhance nasal residence time and improve drug permeation. Such an approach may reduce dosing frequency, improve patient compliance, and enable more stable therapeutic outcomes. Nano-enabled immunomodulatory therapy offers additional potential for disease modification. Nanocarrier systems conjugated with antibodies or ligands targeting CD20-positive B cells may enhance the precision of rituximab delivery while minimizing systemic immunosuppression. Controlled nano-immunotherapy platforms could selectively regulate pathogenic autoantibody production without broadly suppressing immune function, representing a promising direction for future therapeutic innovation.

Despite the potential of nanotechnology in Lambert–Eaton myasthenic syndrome (LEMS), several barriers limit clinical translation.

Efficient delivery to the neuromuscular junction remains challenging due to the restrictive nature of the blood–nerve barrier, requiring careful optimization of nanoparticle size, surface properties, and stability. Immunogenicity is another concern, as nanoparticles may trigger unintended immune responses [87]. This can be mitigated through the use of biocompatible materials and surface modifications such as PEGylation. In addition, large-scale manufacturing remains complex, as consistent control of particle size, drug loading, and release behavior is essential for reproducibility and regulatory compliance. Regulatory approval is further complicated by the need for extensive evaluation of safety, biodistribution, and long-term effects, particularly in rare diseases with limited patient populations. Finally, the lack of clinically validated ligands for precise presynaptic targeting highlights the need for continued research in targeted delivery strategies [88].

8. Risk Factor Mitigation and Epidemiological Considerations

The prevention of Lambert–Eaton myasthenic syndrome remains challenging due to its complex and incompletely understood etiology. However, risk factor mitigation strategies are particularly relevant for the paraneoplastic form of the disease, which is strongly associated with small cell lung carcinoma. Tobacco exposure represents the most significant modifiable risk factor, as it contributes to carcinogenesis through cumulative genetic and epigenetic alterations. Accordingly, smoking cessation and avoidance of second-hand smoke are critical components of risk reduction. Environmental carcinogens, such as radon gas, may further increase oncogenic risk by inducing DNA damage in pulmonary tissue, and therefore, environmental monitoring and mitigation strategies are recommended. From a physiological perspective, factors that influence neuromuscular transmission may modulate symptom severity. Elevated temperatures can impair synaptic efficiency by altering ion channel kinetics and accelerating enzymatic processes, potentially reducing the effective availability of acetylcholine at the neuromuscular junction. Given the underlying deficit in quantal acetylcholine release in LEMS, such thermal effects may exacerbate muscle weakness. In addition, general health optimization strategies—including balanced nutrition, maintenance of healthy body weight, and engagement in moderate physical activity within individual tolerance limits—may support overall neuromuscular function. Adequate rest and stress management are also important, as physiological stressors may worsen symptom burden. Although these measures do not directly prevent disease onset, they contribute to improved functional stability and quality of life in affected individuals.

9. Future Perspectives and Conclusion

Lambert–Eaton myasthenic syndrome continues to pose diagnostic and therapeutic challenges despite notable progress in understanding its clinical and immunological basis. Future advancements will likely depend on improving diagnostic precision through the replacement of conventional radioisotope-based assays with modern, non-radioactive technologies. In this context, emerging platforms such as electrochemical immunosensors and surface plasmon resonance (SPR)-based systems offer significant advantages, including rapid detection, enhanced sensitivity, and potential for point-of-care application. These developments may enable earlier diagnosis and more effective monitoring of disease progression. From a therapeutic perspective, existing treatments remain limited by short drug half-life, fluctuating plasma concentrations, and dose-related adverse effects. Nanotechnology-driven approaches present a promising opportunity to overcome these limitations by enabling controlled drug release, stabilizing pharmacokinetics, and improving delivery efficiency to target sites. Importantly, next-generation theranostic nanoplatforms introduce the possibility of integrating diagnostic capability with treatment delivery. Such systems could enable responsive or “closed-loop” therapeutic strategies, in which drug release is dynamically adjusted based on disease-specific signals, thereby enhancing treatment precision while reducing systemic exposure.

In parallel, progress in immunotherapy and biomarker discovery is expected to support more individualized management strategies. The identification of reliable predictive markers for disease progression, malignancy risk, and treatment responsiveness may facilitate tailored therapeutic decisions. Furthermore, deeper insights into genetic susceptibility and environmental contributors may refine our understanding of disease mechanisms. Although many of these innovations remain in early developmental stages, their combined potential suggests a transition from conventional symptomatic management toward more precise, mechanism-based interventions. Achieving this goal will require coordinated efforts across neurology, immunology, oncology, and nanotechnology disciplines, as well as collaborative clinical research. Ultimately, the integration of advanced diagnostics, targeted immunomodulation, and nanomedicine-based delivery systems may significantly improve long-term outcomes and quality of life for individuals affected by LEMS.

Funding

The authors received no external funding for this work.

CRediT authorship contribution statement

Edward Justus: Visualization, Formal analysis, Data curation. **Jaghatha Therassama:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration. **Somasundaram Arumugam:** Visualization, Investigation, Formal analysis. **Dharmian Jose:** Writing – review & editing, Validation, Investigation, Conceptualization. **Pavazhaviji Pazhani:** Writing – review & editing, Validation, Software, Investigation.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request

References

[1] S. El-Wahsh, S. Reddel, Lambert Eaton Myasthenic Syndrome, Int. Rev. Neurobiol. 182 (Jan. 2025) 227–251, https://doi.org/10.1016/BS.IRN.2025.04.027.
[2] B.J. Drapkin, D.J. Morrell, R. Grebla, G. Shechter, D.E. Gerber, Marked underdiagnosis of Lambert-Eaton myasthenic syndrome in small cell lung cancer: an analysis of real-world claims data, Front. Oncol. 15 (2025), https://doi.org/10.3389/fonc.2025.1650373.
[3] L.M. Eaton, E.H. Lambert, Electromyography and electric stimulation of nerves in diseases of motor unit: Observations on myasthenic syndrome associated with malignant tumors, J. Am. Med. Assoc. 163 (13) (1957) 1117–1124, https://doi.org/10.1001/jama.1957.02970480021005.
[4] H. Handa, et al., Diagnosis of Lambert-Eaton myasthenic syndrome: Muscle fatigue with normal manual muscle testing, areflexia, and electrodiagnostic findings, J. Neuroimmunol. 417 (Aug. 2026), https://doi.org/10.1016/j.jneuroim.2026.578917.
[5] J. Wickel, et al., Anti-CD19 CAR-T cells are effective in severe idiopathic Lambert-Eaton myasthenic syndrome, Cell Rep. Med. 5 (11) (Nov. 2024), https://doi.org/10.1016/j.xcrm.2024.101794.
[6] H. Preßler, I. Haddy, C. Daugherty, V. Postila, A. Meisel, Paraneoplastic Lambert–Eaton myasthenic syndrome associated with non-small cell lung cancer: data from the European LEMS registry and systematic review, Neurol. Res. Pr. 7 (1) (Dec. 2025), https://doi.org/10.1186/s42466-025-00453-5.
[7] M. Motomura, I. Johnston, B. Lang, A. Vincent, J. Newsom-Davis, An improved diagnostic assay for Lambert-Eaton myasthenic syndrome, J. Neurol. Neurosurg. Psychiatry 58 (1) (1995) 85–87, https://doi.org/10.1136/jnnp.58.1.85.
[8] W.R. Bakker, A. Pharmd, L. Remijn-Nelissen, K.J.M. Schimmel, A. Pharmd, M. R. Tannemaat, J.J.G.M. Verschuuren, T. Van Gelder, Pharmacological treatment of Lambert-Eaton Myasthenic Syndrome, MGFA Int. Conf. Proc. (2023).

[9] M.J. Titulaer, et al., Clinical Dutch-English Lambert-Eaton Myasthenic Syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS, J. Clin. Oncol. 29 (7) (2011) 902–908, https://doi.org/10.1200/JCO.2010.32.0440.

[10] M.J. Titulaer, B. Lang, and J.J.G.M. Verschuuren, "Lambert-Eaton myasthenic syndrome: From clinical characteristics to therapeutic strategies," 2011. doi: 10.1016/S1474-4422(11)70245-9.

[11] N.E. Gilhus and J.J. Verschuuren, "Myasthenia gravis: Subgroup classification and therapeutic strategies," 2015. doi: 10.1016/S1474-4422(15)00145-3.

[12] M.J. Titulaer, et al., The Lambert-Eaton myasthenic syndrome 1988-2008: A clinical picture in 97 patients, J. Neuroimmunol. 201–202 (C) (2008) 153–158, https://doi.org/10.1016/j.jneuroim.2008.05.025.

[13] Y.K. Nakao, et al., Seronegative Lambert-Eaton myasthenic syndrome: Study of 110 japanese patients, Neurology 59 (11) (2002) 1773–1775, https://doi.org/10.1212/01.WNL.0000037485.56217.5F.

[14] M.N. Meriggioli, "Use of immunoassays in neurological diagnosis and research," 2005. doi: 10.1179/016164105X49535.

[15] A.M. Stark, H.H. Hugo, H. Tscheslog, H.M. Mehdorn, p53, BCL-2 and BAX in non-small cell lung cancer brain metastases: A comparison of real-time RT-PCR, ELISA and immunohistochemical techniques, Neurol. Res. 29 (5) (2007) 435–440, https://doi.org/10.1179/016164107X165282.

[16] V.A. Lennon, et al., Calcium-Channel Antibodies in the Lambert–Eaton Syndrome and Other Paraneoplastic Syndromes, N. Engl. J. Med. 332 (22) (1995) 1467–1475, https://doi.org/10.1056/nejm199506013322203.

[17] M. Motomura, B. Lang, I. Johnston, J. Palace, A. Vincent, J. Newsom-Davis, Incidence of serum anti-P/Q-type and anti-N-type calcium channel autoantibodies in the Lambert-Eaton myasthenic syndrome, J. Neurol. Sci. 147 (1) (1997) 35–42, https://doi.org/10.1016/S0022-510X(96)05303-8.

[18] N.L. Zalewski, V.A. Lennon, D.H. Lachance, C.J. Klein, S.J. Pittock, A. Mckeon, P/Q- and N-type calcium-channel antibodies: Oncological, neurological, and serological accompaniments, Muscle Nerve 54 (2) (2016) 220–227, https://doi.org/10.1002/mus.25027.

[19] M. Benatar, et al., Presynaptic neuronal antigens expressed by a small cell lung carcinoma cell line, J. Neuroimmunol. 113 (1) (2001) 153–162, https://doi.org/10.1016/S0165-5728(00)00431-8.

[20] M.J. Titulaer, et al., SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: Frequency and relation with survival, J. Clin. Oncol. 27 (26) (2009) 4260–4267, https://doi.org/10.1200/JCO.2008.20.6169.

[21] K.T. Parsons, W.W. Kwok, Linear B-cell epitopes in Lambert-Eaton myasthenic syndrome defined by cell-free synthetic peptide binding, J. Neuroimmunol. 126 (1–2) (2002) 190–195, https://doi.org/10.1016/S0165-5728(02)00063-2.

[22] M. Takamori, K. Komai, K. Iwasa, Antibodies to calcium channel and synaptotagmin in Lambert-Eaton myasthenic syndrome, Am. J. Med. Sci. 319 (4) (2000) 204–208, https://doi.org/10.1016/S0002-9629(15)40731-1.

[23] H.L. Pellkofer, et al., Lambert-Eaton myasthenic syndrome differential reactivity of tumor versus non-tumor patients to subunits of the voltage-gated calcium channel, J. Neuroimmunol. 204 (1–2) (2008) 136–139, https://doi.org/10.1016/j.jneuroim.2008.08.002.

[24] J.J. Verschuuren, et al., Antibodies against the calcium channel β-subunit in Lambert-Eaton myasthenic syndrome, Neurology 50 (2) (1998) 475–479, https://doi.org/10.1212/WNL.50.2.475.

[25] M.J. Titulaer, et al., Screening for tumours in paraneoplastic syndromes: Report of an EFNS Task Force, Eur. J. Neurol. 18 (1) (2011) 19–e3, https://doi.org/10.1111/j.1468-1331.2010.03220.x.

[26] K.G. Henriksson, O. Nilsson, I. Rosén, H.H. Schiller, CLINICAL, NEUROPHYSIOLOGICAL AND MORPHOLOGICAL FINDINGS IN EATON LAMBERT SYNDROME, Acta Neurol. Scand. 56 (2) (1977) 117–140, https://doi.org/10.1111/j.1600-0404.1977.tb01417.x.

[27] M.B. Baslo, F. Deymeer, P. Serdaroglu, Y. Parman, C. Ozdemir, M. Cuttini, Decrement pattern in Lambert-Eaton myasthenic syndrome is different from myasthenia gravis, Neuromuscul. Disord. 16 (7) (2006) 454–458, https://doi.org/10.1016/j.nmd.2006.05.009.

[28] R.W. Tim, D.B. Sanders, Repetitive nerve stimulation studies in the Lambert–Eaton myasthenic syndrome, Muscle Nerve 17 (9) (1994) 995–1001, https://doi.org/10.1002/mus.880170906.

[29] R.W. Tim, J.M. Massey, D.B. Sanders, Lambert-Eaton myasthenic syndrome: Electrodiagnostic findings and response to treatment, Neurology 54 (11) (2000) 2176–2178, https://doi.org/10.1212/WNL.54.11.2176.

[30] S.J. Oh, K. Kurokawa, G.C. Claussen, H.F. Ryan, Electrophysiological diagnostic criteria of Lambert-Eaton myasthenic syndrome, Muscle Nerve 32 (4) (2005) 515–520, https://doi.org/10.1002/mus.20389.

[31] Y. Hatanaka, S.J. Oh, Ten-second exercise is superior to 30-second exercise for post-exercise facilitation in diagnosing Lambert-Eaton myasthenic syndrome, Muscle Nerve 37 (5) (2008) 572–575, https://doi.org/10.1002/mus.20979.

[32] J.H. O'neill, N.M.F. Murray, J. Newsom-davis, The lambert-eaton myasthenic syndrome: A REVIEW of 50 cases, Brain 111 (3) (1988) 577–596, https://doi.org/10.1093/brain/111.3.577.

[33] S. Kohler, A. Meisel, The Lambert-Eaton Myasthenic Syndrome: An Overview | Das Lambert-Eaton-Myasthenie-Syndrom: Ein Überblick, Aktuel-.-. Neurol. 45 (4) (2018).

[34] R. Di Lorenzo, et al., Low specificity of voltage-gated calcium channel antibodies in Lambert–Eaton myasthenic syndrome: a call for caution, J. Neurol. 265 (9) (2018) 2114–2119, https://doi.org/10.1007/s00415-018-8959-8.

[35] F.J. Urbano, M.R. Pagani, and O.D. Uchitel, "Calcium channels, neuromuscular synaptic transmission and neurological diseases," 2008. doi: 10.1016/j.jneuroim.2008.06.031.

[36] A. Pinto, et al., Human autoantibodies specific for the α1A calcium channel subunit reduce both P-type and Q-type calcium currents in cerebellar neurons, Proc. Natl. Acad. Sci. U. S. A. 95 (14) (1998) 8328–8333, https://doi.org/10.1073/pnas.95.14.8328.

[37] J. Spillane, et al., Lambert-Eaton syndrome IgG inhibits transmitter release via P/Q $Ca2+$ channels, Neurology 84 (6) (2015) 575–579, https://doi.org/10.1212/WNL.0000000000001225.

[38] C. Angelini, "Diagnosis and management of autoimmune myasthenia gravis," 2011. doi: 10.2165/11584740-000000000-00000.

[39] M. Takamori, Lambert-Eaton myasthenic syndrome: Search for alternative autoimmune targets and possible compensatory mechanisms based on presynaptic calcium homeostasis, J. Neuroimmunol. 201–202 (C) (2008) 145–152, https://doi.org/10.1016/j.jneuroim.2008.04.040.

[40] M.M. Thomas, S.M.J. Dunn, Amyotrophic lateral sclerosis immunoglobulins are ineffective in altering calcium influx through presynaptic voltage-sensitive calcium channels, Neurol. Res. 19 (2) (1997) 129–134, https://doi.org/10.1080/01616412.1997.11740785.

[41] S.J. Oh, Y. Hatanaka, G.C. Claussen, E. Sher, Electrophysiological differences in seropositive and seronegative Lambert-Eaton myasthenic syndrome, Muscle Nerve 35 (2) (2007) 178–183, https://doi.org/10.1002/mus.20672.

[42] I.M. Fardhani, C. Graciella, M.I.R. Rayyan, Lambert-Eaton Myasthenic Syndrome: A Review of Rare Neuromuscular Disease Related to Paraneoplastic and Autoimmune, AKSONA 5 (1) (2025) 34–42, https://doi.org/10.20473/aksona.v5i1.56359.

[43] Z.U. Kocabas, F. Kizilay, I. Basarici, H. Uysal, Evaluation of cardiac autonomic functions in myasthenia gravis, Neurol. Res. 40 (5) (2018) 405–412, https://doi.org/10.1080/01616412.2018.1446690.

[44] C.A. Sirbu *et al.*, "Orphan Drugs in Neurology—A Narrative Review," 2023. doi: 10.3390/jpm13030420.

[45] J. Newsom-Davis, "Therapy in myasthenia gravis and Lambert-Eaton myasthenic syndrome," 2003. doi: 10.1055/s-2003-41135.

[46] S. Lindquist and M. Stangel, "Update on treatment options for Lambert-Eaton myasthenic syndrome: Focus on use of amifampridine," 2011. doi: 10.2147/NDT.S10464.

[47] J. Kalia, K.J. Swartz, Elucidating the molecular basis of action of a classic drug: Guanidine compounds as inhibitors of voltage-gated potassium channels, Mol. Pharm. 80 (6) (2011) 1085–1095, https://doi.org/10.1124/mol.111.074989.

[48] J. Molgó, H. Lundh, S. Thesleff, Potency of 3,4-Diaminopyridine and 4-aminopyridine on mammalian neuromuscular transmission and the effect of pH changes, Eur. J. Pharm. 61 (1) (1980) 25–34, https://doi.org/10.1016/0014-2999(80)90378-7.

[49] N. Zhang, et al., 3,4-diaminopyridine treatment for Lambert-Eaton myasthenic syndrome in adults: a meta-analysis of randomized controlled trials, BMC Neurol. 21 (1) (2021), https://doi.org/10.1186/s12883-021-02405-3.

[50] H.J. Anderson, H.C. Churchill-Davidson, A.T. Richardson, "BRONCHIAL NEOPLASM WITH MYASTHENIA. PROLONGED APNŒA AFTER ADMINISTRATION OF SUCCINYLCHOLINE,", Lancet 262 (6799) (1953) 1291–1293, https://doi.org/10.1016/S0140-6736(53)91358-0.

[51] J.J.G.M. Verschuuren, P.W. Wirtz, M.J. Titulaer, L.N.A. Willems, and J. Van Gerven, "Available treatment options for the management of Lambert-Eaton myasthenic syndrome," 2006. doi: 10.1517/14656566.7.10.1323.

[52] P.G. Bain, et al., Effects of intravenous immunoglobulin on muscle weakness and calcium- channel autoantibodies in the Lambert-Eaton myasthenic syndrome, Neurology 47 (3) (1996) 678–683, https://doi.org/10.1212/WNL.47.3.678.

[53] M.E. Farrugia and A. Vincent, "Autoimmune mediated neuromuscular junction defects," 2010. doi: 10.1097/WCO.0b013e32833cc968.

[54] M.F. Devine, N. Kothapalli, M. Elkhooly, and D. Dubey, "Paraneoplastic neurological syndromes: clinical presentations and management," 2021. doi: 10.1177/1756286420985323.

[55] I. Elovaara *et al.*, "EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases," 2008. doi: 10.1111/j.1468-1331.2008.02246.x.

[56] M. Sharbafshaaer, G. Cirillo, F. Esposito, G. Tedeschi, and F. Trojsi, "Harnessing Brain Plasticity: The Therapeutic Power of Repetitive Transcranial Magnetic Stimulation (rTMS) and Theta Burst Stimulation (TBS) in Neurotransmitter Modulation, Receptor Dynamics, and Neuroimaging for Neurological Innovations," 2024. doi: 10.3390/biomedicines12112506.

[57] S.J. Oh, Amifampridine for the treatment of Lambert-Eaton myasthenic syndrome, Expert Rev. Clin. Immunol. 15 (10) (2019), https://doi.org/10.1080/1744666X.2020.1670061.

[58] C. Toader, A.V. Dumitru, L. Eva, M. Serban, R.A. Covache-Busuioc, and A.V. Ciurea, "Nanoparticle Strategies for Treating CNS Disorders: A Comprehensive Review of Drug Delivery and Theranostic Applications," 2024. doi: 10.3390/ijms252413302.

[59] A. Zeb, M. Gul, T.T.L. Nguyen, and H.J. Maeng, "Controlled release and targeted drug delivery with poly(lactic-co-glycolic acid) nanoparticles: reviewing two decades of research," 2022. doi: 10.1007/s40005-022-00584-w.

[60] S.J. Oh, Amifampridines are the Most Effective Drugs for Treating Lambert-Eaton Myasthenic Syndrome With a Focus on Pediatric Lambert-Eaton Myasthenic Syndrome, Jul. 01, Korean Neurol. Assoc. (2024), https://doi.org/10.3988/jcn.2024.0018.

[61] M.A. Krishnan, et al., Engineering Neurotoxin-Functionalized Exosomes for Targeted Delivery to the Peripheral Nervous System, Pharmaceutics 16 (1) (Jan. 2024), https://doi.org/10.3390/pharmaceutics16010102.

[62] A.M. Martins, R. Palomba, M. Schlich, P. Decuzzi, On the axonal transport of lipid nanoparticles in primary hippocampal neurons, J. Drug Deliv. Sci. Technol. 101 (Nov. 2024), https://doi.org/10.1016/j.jddst.2024.106282.
[63] V. Kumar, S. Sharma, A. Singh, Nanoparticles: a new frontier in neurodegenerative disease therapy, Front. Media SA (2025), https://doi.org/10.3389/fmedt.2025.1654003.
[64] C. Kaur, E. Villarreal, M.H. Cabe, K.A. Langert, Blood nerve barrier permeability enables nerve targeting of circulating nanoparticles in experimental autoimmune neuritis, Sci. Rep. 15 (1) (Dec. 2025), https://doi.org/10.1038/s41598-025-96231-z.
[65] J. López-Espinosa, P. Park, M. Holcomb, B. Godin, and S. Villapol, "Nanotechnology-driven therapies for neurodegenerative diseases: a comprehensive review," 2024. doi: 10.1080/20415990.2024.2401307.
[66] L.T.T. Nguyen, V.A. Duong, Nose-to-Brain Drug Delivery, Encyclopedia 5 (3) (2025), https://doi.org/10.3390/encyclopedia5030091.
[67] A. Yousfan, M.J. Al Rahwanji, A. Hanano, H. Al-Obaidi, A Comprehensive Study on Nanoparticle Drug Delivery to the Brain: Application of Machine Learning Techniques, Mol. Pharm. 21 (1) (2024), https://doi.org/10.1021/acs.molpharmaceut.3c00880.
[68] A. Yousfan, et al., Innovative Microencapsulation of Polymyxin B for Enhanced Antimicrobial Efficacy via Coated Spray Drying, Mol. Pharm. (2024), https://doi.org/10.1021/acs.molpharmaceut.4c00594.
[69] L. Pineiro-Alonso, I. Rubio-Prego, A. Lobyntseva, E. González-Freire, R. Langer, and M.J. Alonso, "Nanomedicine for targeting brain Neurodegeneration: Critical barriers and circadian rhythm Considerations," 2025. doi: 10.1016/j.addr.2025.115606.
[70] C. Saraiva, J. Paiva, T. Santos, L. Ferreira, L. Bernardino, MicroRNA-124 loaded nanoparticles enhance brain repair in Parkinson's disease, J. Control. Release 235 (2016), https://doi.org/10.1016/j.jconrel.2016.06.005.
[71] V.K. Yadav *et al.*, "Recent advances in nanotechnology for Parkinson's disease: diagnosis, treatment, and future perspectives," 2025. doi: 10.3389/fmed.2025.1535682.
[72] V.P. Torchilin, "Recent advances with liposomes as pharmaceutical carriers," 2005. doi: 10.1038/nrd1632.
[73] V.P. Torchilin, "Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery," 2014. doi: 10.1038/nrd4333.
[74] J.X. Si, Z.C. Liu, F. Gu, X. Jin, and Y.Y. Ma, "Nanoparticle-based delivery systems for targeted therapy in brain tumors: Progress, challenges and perspectives (Review)," 2025. doi: 10.3892/ijo.2025.5789.
[75] R. Lombardo, et al., Development of Lyophilised Eudragit® Retard Nanoparticles for the Sustained Release of Clozapine via Intranasal Administration, Pharmaceutics 15 (5) (2023), https://doi.org/10.3390/pharmaceutics15051554.
[76] S. Adwan, T. Obeidi, F. Al-Akayleh, Chitosan Nanoparticles Embedded in In Situ Gel for Nasal Delivery of Imipramine Hydrochloride: Short-Term Stage Development and Controlled Release Evaluation, Polym. (Basel) 16 (21) (2024), https://doi.org/10.3390/polym16213062.
[77] E.S. Khoury, et al., Dendrimer nanotherapy targeting of glial dysfunction improves inflammation and neurobehavioral phenotype in adult female Mecp2-heterozygous mouse model of Rett syndrome, J. Neurochem. 168 (5) (2024), https://doi.org/10.1111/jnc.15960.
[78] C.L. Nemeth, et al., Targeted Brain Delivery of Dendrimer-4-Phenylbutyrate Ameliorates Neurological Deficits in a Long-Term ABCD1-Deficient Mouse Model of X-Linked Adrenoleukodystrophy, Neurotherapeutics 20 (1) (2023), https://doi.org/10.1007/s13311-022-01311-x.
[79] D. Stanicki, T. Vangijzegem, I. Ternad, and S. Laurent, "An update on the applications and characteristics of magnetic iron oxide nanoparticles for drug delivery," 2022. doi: 10.1080/17425247.2022.2047020.
[80] N. Saikia, "Inorganic-Based Nanoparticles and Biomaterials as Biocompatible Scaffolds for Regenerative Medicine and Tissue Engineering: Current Advances and Trends of Development," 2024. doi: 10.3390/inorganics12110292.
[81] N.G. Khlebtsov, L.A. Dykman, B.N. Khlebtsov, Synthesis and plasmonic tuning of gold and gold–silver nanoparticles, Russ. Chem. Rev. 91 (10) (2022), https://doi.org/10.57634/rcr5058.
[82] G.P. Lachance, É. Boisselier, M. Boukadoum, A. Miled, Towards an advanced neurotechnological system: Colorimetric sensing with a novel grism-based spectrometer, functionalized gold nanoparticles and a heterogeneous embedded system, Philos. Trans. R. Soc. A Math. Phys. Eng. Sci. 380 (2228) (2022), https://doi.org/10.1098/rsta.2021.0016.
[83] A. Marcotti, et al., Triamcinolone-loaded nanocarriers: a novel strategy to mitigate cognitive and emotional sequelae induced by traumatic brain injury via modulation of oxidative stress, Front. Behav. Neurosci. 19 (2025), https://doi.org/10.3389/fnbeh.2025.1638417.
[84] M.D. Cayero-Otero, et al., Venlafaxine-PLGA nanoparticles provide a fast onset of action in an animal model of depression via nose-to-brain, Int. J. Pharm. 678 (2025), https://doi.org/10.1016/j.ijpharm.2025.125692.
[85] J. Majumder, T. Minko, Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery, Taylor Fr. Ltd (2021), https://doi.org/10.1080/17425247.2021.1828339.
[86] X. jian Dai, W.J. Li, D.D. Xie, B. xia Liu, L. Gong, H.H. Han, Stimuli-Responsive Nano Drug Delivery Systems for the Treatment of Neurological Diseases, Mar. 05, John Wiley and Sons Inc, 2025, https://doi.org/10.1002/smll.202410030.
[87] Y. Herdiana, Bridging the Gap: The Role of Advanced Formulation Strategies in the Clinical Translation of Nanoparticle-Based Drug Delivery Systems, Dove Med. Press Ltd (2025), https://doi.org/10.2147/IJN.S554821.
[88] K. Wang, R. Yang, J. Li, H. Wang, L. Wan, J. He, Nanocarrier-based targeted drug delivery for Alzheimer's disease: addressing neuroinflammation and enhancing clinical translation, Front. Media SA (2025), https://doi.org/10.3389/fphar.2025.1591438.