

Motor neurone disease: progress and challenges

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Motor neurone disease (MND) is a progressive, neurodegenerative disorder that mainly attacks the human motor system, leading to significant disability and ultimately death, usually within 3 years.¹ The incidence of MND in Western populations, including Australia, is about 2–3 per 100 000, with a national prevalence of about 8 per 100 000.² Currently, 1500 Australian patients suffer from the disease.³ As there remains no test for MND, diagnosis is based on clinical findings, supported by investigations such as neurophysiological testing and structural imaging to exclude mimic disorders.⁴ Given that MND is clinically and pathologically heterogeneous, therapeutic and neuro-protective targets have been difficult to identify. However, progress in recent years has stimulated innovative research into this devastating disorder. In this review, we discuss areas of progress in the field of MND, including improved understanding of the various clinical phenotypes, the development of standards of care, the continuum with frontotemporal dementia (FTD), the role of genetics, and the global clinical trials pipeline. We also highlight the importance of translating research into clinical practice through various networks.

To formulate an evidence-based review of MND in clinical practice, we searched PubMed for original and review articles published between 1990 and 2016, focusing on publications within the past 5 years. We also sourced guidelines and other articles from MND Australia and the Cochrane Database of Systematic Reviews, and drew on collective specialist experience across Australia's multidisciplinary clinics.

New clinical perspectives

Patients with MND are heterogeneous with varied presentations, depending on the site of disease onset. The definitive clinical characteristics remain the presence of upper and lower motor neurone signs coexisting in the same symptomatic area (Box 1).^{3,5} The median time to diagnosis is about 14 months, which is often a distressing period that also inevitably delays appropriate disease-modifying therapies and acceptance of prognosis.^{4,6}

The clinical phenotype and site of disease onset appears to be of important prognostic significance in MND.⁷ Four main clinical phenotypes are described based on the relative degree of upper and lower motor neurone predominance and the site of onset:

- Amyotrophic lateral sclerosis (ALS) represents 70% of cases.^{3,6} ALS classically begins in the limb and exhibits a combination of upper and lower motor neurone signs.^{3,6} In about 20% of patients, the weakness starts in the bulbar region.³ With a median survival of about 3 years, ALS is the most malignant of the MND phenotypes.⁷
- Isolated bulbar palsy represents about 4–8% of cases.⁸ Patients have localised, progressive speech and swallowing difficulties for a prolonged period (> 6 months), despite relative preservation of limb strength. Although almost all isolated bulbar palsy patients eventually progress to definite

Summary

- Major progress has been made over the past decade in the understanding of motor neurone disease (MND), changing the landscape of this complex disease.
- Through identifying positive prognostic factors, new evidence-based standards of care have been established that improve patient survival, reduce burden of disease for patients and their carers, and enhance quality of life. These factors include early management of respiratory dysfunction with non-invasive ventilation, maintenance of weight and nutritional status, as well as instigation of a multidisciplinary team including neurologists, general practitioners and allied health professionals.
- Advances in technology have enhanced our understanding of the genetic architecture of MND considerably, with implications for patients, their families and clinicians. Recognition of extra-motor involvement, particularly cognitive dysfunction, has identified a spectrum of disease from MND through to frontotemporal dementia.
- Although riluzole remains the only disease-modifying medication available in clinical practice in Australia, several new therapies are undergoing clinical trials nationally and globally, representing a shift in treatment paradigms. Successful translation of this clinical research through growth in community funding, awareness and national MND research organisations has laid the foundation for closing the research–practice gap on this debilitating disease.
- In this review, we highlight these recent developments, which have transformed treatment, augmented novel therapeutic platforms, and established a nexus between research and the MND community. This era of change is of significant relevance to both specialists and general practitioners who remain integral to the care of patients with MND.

ALS, they have a better prognosis than bulbar-onset ALS, with disease duration extended by at least 12 months.⁸

- Progressive muscular atrophy presents with pure lower motor neurone signs and represents 5% of the MND phenotype.⁹ A subgroup develops a flail limb variant, in which symptoms are limited either to the upper (flail arm syndrome) or the lower limbs (flail leg syndrome) for at least 12 months. The prognosis for these variants is typically more prolonged than for classic ALS, but patients with more generalised weakness (> 50% of limb regions affected) follow a similar disease course to ALS.⁹
- Primary lateral sclerosis (1–3% of cases)¹⁰ presents with pure upper motor neurone signs and a predilection for lower limb disease onset. Patients experience a much slower disease progression and better prognosis, with some known to have normal life expectancy.¹⁰

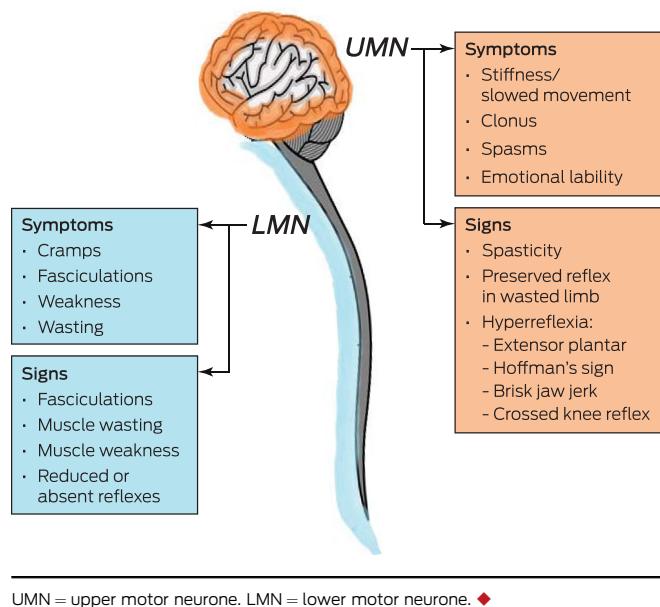
Advances in treatment approach: new standards of care

An increased understanding of this complex disorder has enabled identification of several important factors that improve survival

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1 Clinical signs and symptoms of upper and lower motor neurone involvement in motor neurone disease



and reduce patient symptoms, generating new evidence-based treatment interventions.¹¹

Multidisciplinary care

Multidisciplinary care has been reported to improve both quality of life and survival, potentially up to 7–24 months.^{12,13} For patients with bulbar disease, survival benefit is possibly even longer.¹² The care team involves medical, nursing and allied health professionals, and focuses on proactive intervention for early holistic management of the patient (Box 2). The network also includes input from MND Australia and state-based associations, which assist with care coordination, family support and community education. This dynamic framework addresses the complex medical issues that arise over time, allows for continual assessment of functional disabilities and psychosocial burden, and provides a network of support for the treating clinicians.¹³ Management within a multidisciplinary care clinic is therefore recommended for all patients, with such clinics operating in most capital cities around Australia.² Telemedicine services are also available in some areas for patients who have attendance difficulties (such as due to disability or location).

Respiratory management with non-invasive ventilation

The benefit of using non-invasive positive pressure ventilation for respiratory involvement has been a crucial discovery in MND care, not only because it greatly improves symptoms and quality of life, but because it extends patient survival by up to 13 months.^{14,15} Only a small proportion of patients with MND have respiratory problems at the initial onset of disease, but almost all will develop symptoms during the course of the disease and most will die from respiratory complications.^{16,17} Respiratory symptoms should therefore be assessed at each visit and, if tolerated, early institution of non-invasive positive pressure ventilation should be implemented.

Nutritional support

Weight loss and malnutrition during the course of disease exert a negative effect on survival, associated with more rapid disease progression.¹⁸ This can occur from development of a hypermetabolic state, swallowing problems, neuropsychiatric issues, and

feeding difficulties due to loss of limb function.¹⁹ Monitoring patients for weight loss is thus essential, and managing this with the help of an experienced speech pathologist and dietitian is critical in routine MND care. Interventions for enteral feeding options (such as percutaneous endoscopic gastrostomy tubes) are helpful in circumventing dysphagia (especially in patients with bulbar-onset MND) and for maintaining nutrition in patients using long term ventilatory support.^{20,21}

Other symptoms

Cumulative experience has guided current clinical practice for the treatment of other symptoms often experienced by patients with MND related to their progressive motor and non-motor dysfunction (Box 3).

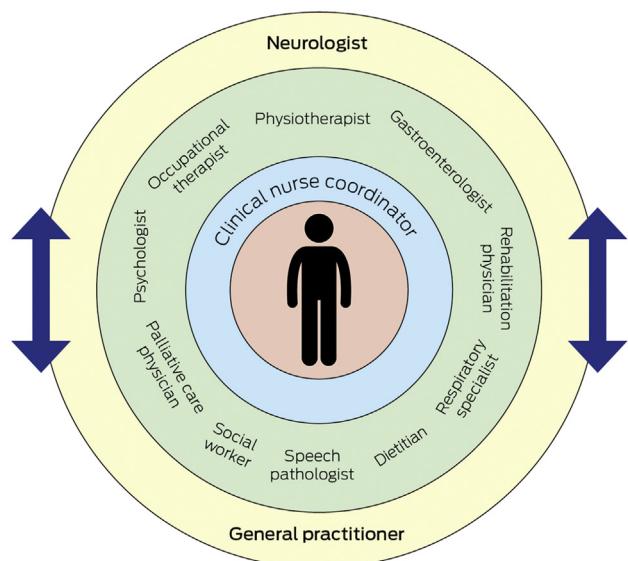
End-of-life challenges

For all patients with MND, the issue of advanced care planning needs to be raised within an appropriate timeframe by the multidisciplinary care team. Although the end-of-life phase remains poorly defined and timing of palliative care input is not consistent globally,²² advance care planning assists patients and their families with important decision making, imparting control and composure in a situation in which they may otherwise be absent. Carers have identified disease-specific advanced directives (such as patient letters of future care) as useful tools to stimulate such discussion while maintaining respect for patient autonomy.²³ Appropriate timing for these discussions is often individually based, but can be sensitively approached when introducing intervention options such as non-invasive positive pressure ventilation or gastrostomy.

The MND–FTD spectrum

Although originally thought to be a purely motor disorder, MND has been increasingly recognised for its extra-motor manifestations. Cognitive impairment is common and may develop in up to

2 Motor neurone disease management: multidisciplinary care model



The multidisciplinary care model centres on the patient with motor neurone disease. It involves dynamic integration of medical, nursing and allied health professionals for optimal patient management. Care is often coordinated by the clinical nurse, with the neurologist and general practitioner overseeing all aspects of care. ♦

3 Symptomatic treatments for motor neurone disease

Symptom	Pharmacological management (first-line medications)	Non-pharmacological management
Secondary to motor dysfunction		
Cramps/fasciculations	Magnesium; carbamazepine	Physiotherapy (stretches); massage; hydrotherapy
Spasticity	Baclofen; clonazepam	Physiotherapy; hydrotherapy
Dyspnoea	Morphine (oral)*; lorazepam	Ventilatory support (respiratory review); chest physiotherapy; manually assisted coughing
Thickened saliva	Normal saline nebulisers; nebulised mucolytics (eg, N-acetylcysteine)	Natural mucolytics (papaya, pineapple, dark grape juice); hydration; portable suction device
Excess (watery) saliva	Amitriptyline; atropine (sublingual)*; glycopyrrolate	Portable suction device; diligent mouth care
Laryngospasm/paroxysmal choking	Lorazepam (sublingual)*; morphine (oral)*	Careful positioning; suctioning; ± ventilatory support
Secondary to non-motor dysfunction		
Pain [†]	Musculoskeletal: paracetamol; ibuprofen Neuropathic: gabapentin, pregabalin	Physiotherapy; hydrotherapy; pressure area care (repositioning, pressure cushion/mattress)
Cognitive dysfunction	Memantine [‡] ; antidepressants	Education of caregivers/family
Emotional lability; depression	Amitriptyline; citalopram; mirtazapine	Psychological support; cognitive behavioural therapy
Sleep disturbance	Amitriptyline; benzodiazepines	Address underlying problem; may need respiratory review ± non-invasive ventilation
Constipation	Aperients; suppositories	Dietary changes (increased fibre and fluid); review drug adverse effects

* The specific formulation indicated is preferred for treatment of this symptom. † Pain is often multifactorial, and treatment must therefore be tailored to the individual cause(s).

‡ Used off label, but not supported by a recent negative phase 3 trial in FTD (Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2013; 12: 149-156). ◆

50% of patients, manifesting as language abnormalities and mild to moderate frontal dysfunction.²⁴ The presence of cognitive impairment is associated with a negative impact on survival, more rapid disease progression, decreased functional ability, higher rates of non-compliance with therapy, and increased psychosocial distress and burden for carers.²⁴

About 15% of patients with MND who have cognitive impairment meet the criteria for FTD, and are considered to have MND–FTD.²⁵ MND and FTD are known to share distinct clinical, neuropathological and genetic features, and it is now recognised that they are part of a continuum in which pure MND (with no cognitive involvement) and pure FTD (with no motor involvement) form ends of a spectrum.²⁵ In 2011, the discovery of a mutation in the *C9orf72* gene unambiguously linked these two conditions (Box 4).^{26,27} *C9orf72* mutation is a hexanucleotide repeat expansion, now known to be responsible for about 40% of familial MND, 25% of familial FTD, and up to 80% of MND–FTD cases.²⁷

Genetics: new insights

The recent discovery of novel genes associated with MND has changed the genetic landscape and encouraged the possibility of future gene therapy. Increasingly, this is modifying the clinical approach to MND, and clinicians commonly face questions regarding genetic causes, testing and family risk. Although mainly driven by the neurologist and clinical geneticist, the dilemma on handling such queries necessitates an understanding of appropriate genetic testing options and counselling for patients and their relatives.

Both familial and sporadic MND are clinically similar, and the genetic and biological distinction between them is also becoming increasingly blurred. Ninety per cent of MND cases appear to be sporadic, with 5–10% of patients having a family history of

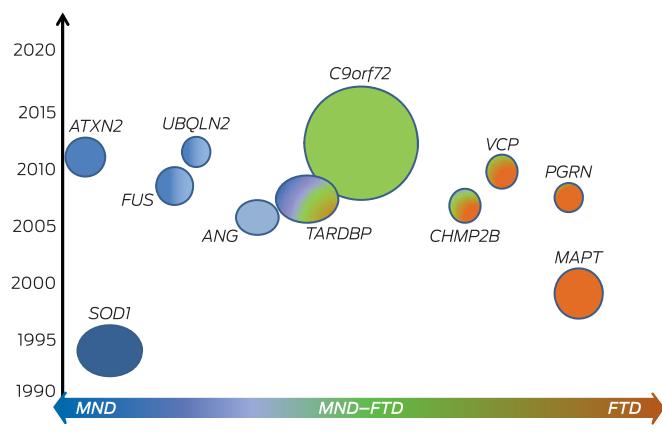
MND.²⁸ Family history is established with the presence of MND or FTD in a first- or second-degree relative. This is most commonly inherited in an autosomal dominant manner but may be autosomal recessive or X-linked.²⁹ Empirical data suggest that the lifetime risk of MND in first-degree relatives of sporadic patients is 1–3%, with a lower risk for second-degree relatives and no apparent increase in risk for more distant relations.³⁰ However, many factors can complicate the pattern and presence of inheritance, including incomplete family information, false paternity, early death and non-penetrance.

To date, more than 25 MND genes have been discovered, explaining 10% of sporadic and 65% of familial disease.³¹ The *C9orf72* repeat expansion is the most common genetic cause of MND. This is reported to account for about 40% of familial and about 7% of sporadic disease,^{31,32} but the exact frequency of MND-related genes varies between different populations and specific data on prevalence in Australia are still limited. Preliminary national studies identified *C9ORF72* mutation in 38.5% of familial cases and 3.5% of sporadic cases.³³ There are also some shared clinical traits in these patients, who are typically of northern European descent and who clinically often have neuropsychiatric symptoms, including frank FTD.^{32,33} There is also a suggestion of higher frequency of bulbar-onset disease, earlier age of symptom onset, and more rapid disease progression.^{26,32}

Who should be offered testing?

Currently, as there is no proven lifestyle modification or medication to reduce the risk of disease, the reason for genetic testing is mainly to provide diagnostic support or pre-natal counselling.³⁴ The option for testing is usually offered by a neurologist to symptomatic patients who have a first- or second-degree relative with MND, FTD or MND–FTD. It can also be discussed with all other symptomatic patients, but with emphasis on the uncertainties of testing. Guidelines do not recommend that

4 The motor neurone disease (MND)–frontotemporal dementia (FTD) spectrum, showing some major known genetic causes (circles) and approximate year of gene discovery



asymptomatic at-risk people be routinely offered testing, particularly as positive test results do not reliably correlate with disease development, severity, progression or age of disease onset.³⁴

Genetic testing options

Until recently, testing was limited to a single gene — *SOD1*. Multigene next-generation sequencing panels and whole-exome sequencing in particular have significantly increased the identification of new genes and commercial testing options. Most tests take from 3–24 weeks for results. Although some genetic services may provide subsidised testing for several MND-related genes, there is no Medicare rebate for testing. The test can therefore cost between \$250 and \$9000, depending on the test and the laboratory.^{25,33}

Limitations of testing

Despite the increase in genetic understanding of disease, establishing genetic testing guidelines has been complicated because of areas of persisting uncertainty. Establishing whether a mutation is pathogenic can be difficult, even for widely studied genes.³⁴ There are also high rates of variants of uncertain significance in multigene panels, and technical challenges from differing laboratory techniques also generate problems.³⁵ These limitations in testing should be emphasised to the patient, including the fact that positive results do not predict disease course, negative results do not exclude genetic basis of disease, and results may not provide interpretable information if a genetic variant of uncertain significance is identified.

Genetic counselling

Given the complications, interpreting results correctly and counselling patients with accurate risk assessments can be difficult. Genetic counselling should be managed by the multidisciplinary team, mainly via a clinical geneticist, but also involving a neurologist, general practitioner and psychologist. Genetic counselling clinics operate across Australia (information is available at <http://www.genetics.edu.au>). Patients and family members should have pre-test consultation with a genetics counsellor as a prerequisite before undergoing a test. Post-test counselling is usually offered for patients with a positive test result, and implications for family members (including offspring) can be discussed.

DNA banking permits future testing and is an option for families who do not feel ready to undergo genetic testing.^{32,34}

Neuroprotection: current and future

Riluzole currently remains the only neuroprotective medication available for patients with MND, and early commencement is recommended for all patients.^{36,37} Riluzole modulates sodium channels and inhibits glutamate release, providing a survival benefit of about 3–6 months, potentially greater for patients with bulbar-onset disease.³⁸ It has a modest side effect profile and is generally well tolerated by patients. Liver function tests and a full blood count should be carried out monthly for 3 months, and 3-monthly thereafter, with treatment cessation if liver function test results (alanine transaminase and aspartate transaminase levels) exceed more than five times the upper limit of normal and/or neutropenia develops.^{37,39}

Current trials

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a free radical scavenger that has gained attention as a potential agent to slow disease progression in MND. Originally approved in Japan in 2002 to treat ischaemic stroke, edaravone has been shown to have multiple effects on the neural and vascular ischaemic cascade.⁴⁰ Although an initial phase 3 randomised controlled trial in MND found no clinically significant effect, a subgroup of mildly symptomatic MND patients who had a forced vital capacity $\geq 80\%$ and who were not more than 2 years from symptom onset showed slowing of disease progression.⁴¹ Intravenous edaravone treatment for such patients was approved in Japan in 2015. An oral equivalent is currently being tested in Europe in a phase 2 trial (<http://www.treeway.nl/news-treeway-announces-positive-data-phase-1-trial-tw001>).

There have been several other phase 3 randomised control trials that have shown promising results. A 2015 trial of ultra-high dose methylcobalamin showed a dose-dependent prolongation of survival when used early in disease.⁴² Positive results have also been seen with masitinib, an oral tyrosine kinase inhibitor that targets macrophages and mast cells,⁴³ and a current trial has shown improvement in patients' Revised ALS Functional Rating Scale scores and forced vital capacity (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-024423-24/IE#E>). Although not available for use in Australia, masitinib has recently been granted orphan drug status by the European Medicines Agency and by the United States Food and Drug Administration (<https://alsnewstoday.com/news-posts/2016/08/11/ab-science-potential-als-treatment-masinib-named-orphan-drug-by-ema>).

In Australia, three human clinical trials are currently commencing in Sydney and Melbourne. The first will analyse central nervous system copper treatment in patients with MND, after delivery of a copper compound (CuATSM) into the central nervous system of *SOD1(G93A)* mouse models prolonged survival by 18 months.⁴⁴ The second trial is a phase 2 study assessing the effects of the antiretroviral agent Triumeq (ViiV Healthcare; combination tablet containing 600 mg abacavir, 300 mg lamivudine and 50 mg dolutegravir) in treating MND. The basis for this trial relates to links between human endogenous retrovirus K and the development of MND in mouse models and in humans.⁴⁵ The third trial is a randomised crossover study evaluating the efficacy of oral FLX-787 (Flex Pharma) — a constituent of ginger — for patients with MND suffering from muscle cramps and spasticity. This study hypothesises that FLX-787 activates transient receptor potential ion channels involved in pain, and indirectly decreases motor neurone hyperexcitability.⁴⁶ Recruitment for these trials began at involved centres towards the end of 2016.

Gene therapy

Gene technology aims to protect motor neurones by modulating mutated gene expression and reducing toxic RNA and proteins. Encouragingly, studies in *SOD1* mouse models have shown significant benefits,⁴⁷ with *C9orf72* studies ongoing. However, this area is still in its infancy, mainly due to the complexity of the MND genetic environment, the difficulty in correlating mutations with clinical pathogenicity, the technical difficulty of the treatment itself, and the economic challenge it presents.⁴⁷

Stem cell therapy

The benefit of stem cell therapy is frequently questioned by patients and families. The efficacy of this treatment remains open in the literature, with small phase 2 trials from around the world reporting safety and efficacy using various modes of stem cell delivery.⁴⁸ Human induced pluripotent stem cell technology is a new and evolving field in which cells are created from patients with MND and differentiated into relevant cell subtypes, such as motor neurones and astrocytes. This has been used in vitro and in mouse models, but engraftment into patients with MND for therapeutic benefit remains a challenge.⁴⁹ Although some countries offer therapeutic trials of stem cell treatment, it is not offered in Australia owing to its unclear efficacy. More understanding of underlying mechanistic processes and long term safety data are needed before clinical translation will be possible.

Fundraising, awareness and research

While the search for improved therapies continues, strong patient advocacy and home-based assistance has been provided by state-based MND associations and MND Australia. The Australian Motor Neurone Disease Registry also collects information from MND centres across Australia to increase clinical understanding and improve quality of care.²

Support for trials in Australia is also needed to drive national research and provide Australian patients with access to potential international treatments. Recently, Australian Clinical Trials and Translational Research Advisory (<https://curemnd.org.au/meet-the-team>) has been established to enable collaboration and grant this much needed opportunity to patients. Increase in community awareness (through campaigns such as the “ice bucket challenge”) and the generation of funding in Australia via organisations such as Cure for MND Foundation (<https://www.curemnd.org.au>) and the MND Research Institute of Australia (MNDRIA) (<http://www.mndaustralia.org.au>) has supported MND national research in an unprecedented way, and is enabling successful translation of research by clinicians into the MND community.

Conclusion

Recent evolution in the clinical, pathological and genetic understanding of MND is progressively unmasking the multifactorial nature of this complex condition. Up-to-date knowledge of the current climate is thus essential for optimal patient care. Closing the research-practice gap through growth of community awareness and support from MND organisations has also been critical for this process. Ongoing engagement of professionals and the community is an invaluable asset to patients, encouraging novel therapeutic strategies and powering the drive to find effective treatments.

Acknowledgements: Thanuja Dharmadasa is a recipient of an Australian Postgraduate Award (University of Sydney), a Rotary Club of Cronulla Funding Partner Scholarship, a MNDRIA PhD Top-up Grant and a Yulgilbar Foundation Alzheimer's Research Program PhD Top-up Award. Matthew Kiernan is the Editor-in-Chief of the *Journal of Neurology, Neurosurgery and Psychiatry*. This work was supported by funding to ForeFront, a collaborative research group dedicated to the study of FTD and MND, from a National Health and Medical Research Council of Australia program grant (1037746).

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed. ■

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