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Tourette's syndrome: IV. Research Landscape and Future Developments

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

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***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

Research design in Tourette's syndrome is complicated by the inherently changing nature of its core symptoms so that current clinical practice is put into question. While research knowledge has advanced in several areas (genetics, neuroimaging, neuropathology, and neurophysiology), questions still remain about how best to classify the syndrome and how closely it is related to other movement or psychiatric disorders. In this article, I review the directions of current and future research in this field as well as research on rare diseases in the U.S. and Europe. I outline the limitations and needs of current research and formulate suggestions for future research. This synoptic view aims to provide a common framework for promoting research on this definitely under-researched clinical pathology.

Abbreviations

AAN: American Academy of Neurology; AAV: Adeno Associated Virus; ADHD: Attention-Deficit Hyperactivity Disorder; AMP®: Accelerating Medicines Partnership®; BGTC: Bespoke Gene Therapy Consortium; BPN: Blueprint Neurotherapeutics Network; CBD: Cannabidiol; CBIT: Comprehensive Behavioral Intervention Therapy; CDC&P: Centers for Disease Control & Prevention CNP: Chronic Neuropathic Pain; DBS: Deep Brain Stimulation; DHHS: Department of Health & Human Services; DS: Dravet's syndrome; DSM: (AAN's) Diagnostic & Statistical Manual of Mental Diseases; EC: European Commission; EJPRD: European Joint Program on Rare Diseases; EMTICS: European Multicentre Tics in Children Studies; ERN: European Reference Networks; ERDRI: European Rare Diseases Registries Infrastructure; FDA: Food & Drug Administration; GARD: Genetic and Rare Diseases; HCP: Human Connectome Project; HPO: Human Phenotype Ontology; IND: Investigational New Drug; IRDRC: International Rare Diseases Research Consortium; NCATS: National Center for Advancing Translational Sciences; NICHHD: (Eunice Kennedy

Shriver) National Institute of Child Health and Human Development; NIDA: National Institute on Drug Abuse; NIDOCD: National Institute on Deafness and Other Communication Disorders; NIH: National Institutes of Health; NIMH: National Institute of Mental Health; NINDS: National Institute of Neurological Disorders and Stroke; NLM: National Library of Medicine; NORD: National Organization for Rare Disorders; ODR: Orphan Drug Regulation; OCD: Obsessive-Compulsive Disorder; RaDaR: Rare Diseases Registry Program; RCT: Randomized Controlled Trials; RDCN: Rare Diseases Clinical Research Network; TAA: Tourette Association of America; TAA IGC: TAA International Genetics Consortium; THC: Tetrahydrocannabinol; TIC-G: Tourette International Collaborative Genetics Study; TMS: Transcranial Magnetic Stimulation; TRND: Therapeutics for Rare and Neglected Diseases.

Keywords

Attention-deficit hyperactivity disorder; Comprehensive behavioral intervention therapy; Deep-brain stimulation; Human connectome; Human phenotype ontology; Neglected diseases; Obsessive-compulsive disorder; Rare disorders; Tourette's syndrome; Transcranial magnetic stimulation.

Introduction

The inherently changing nature of the core symptoms of Tourette's syndrome (TS) complicates the research design in that field, resulting in questions about treatment in clinical practice. Results from case studies may not be borne out by controlled or prospective longitudinal studies. Further, alternative therapies involving unstudied efficacy and side effects are pursued by many parents.

Since 1999, research has advanced knowledge of TS in the areas of genetics, neuroimaging, neuropathology, and neurophysiology, but questions remain about how best to classify the syndrome and how closely it is related to other movement or psychiatric disorders. Modeled after the genetic breakthroughs seen with large-scale efforts in other neurodevelopmental disorders, three groups are collaborating in research of the genetics of TS: The Tourette Syndrome Association International Consortium for Genetics (TSA ICG); the Tourette International Collaborative Genetics Study (TIC-Genetics); and the European Multicentre Tics in Children Studies (EMTICS). However, compared to the progress made in gene discovery in certain neurodevelopmental or mental health disorders (autism, schizophrenia and bipolar disorder), the scale of related TS research is lagging due to insufficient funding.

In this article, I review the directions of current and future TS research as well as research on rare diseases in the U.S. and Europe. I outline the limitations and needs of current research and formulate some suggestions for future research. Lastly, I will encourage patients and others to participate in, and advocate the pursuit of, research. This synoptic view aims to provide a common framework with the view to promote research on this definitely under-researched clinical pathology.

Directions of current and future TS research

The direction of current and future research in TS was aptly outlined in a 2005 journal article by Dr., Neal N. Swerdlow, the outgoing chairman of the Scientific Advisory Board of the Tourette Syndrome Association (TSA) [now renamed Tourette Association of America (TAA)]. He divided the research landscape into five broad questions about TS, namely: What is it? Who has it? What causes it? How should it be studied? and How should it be (medically) treated? Thus:

What is TS?

According to Swerdlow, "the 'core' TS conundrum" is a “lack of consensus about the definition of TS”. Since

vocal tics result from a motor event (i.e., a contracting diaphragm moving air through the upper airways), TS could be defined as a disorder of motor tics, eliminating the distinction between TS and the other tic disorders. Further, individuals who have only tics may not be functionally impaired, raising the question of whether TS, as currently defined, should be a diagnosis in the American Academy of Neurology (AAN)'s Diagnostic and Statistical Manual of Mental Disorders (DSM).

Swerdlow further highlighted the importance of studies in new areas such as behavioral techniques and says that *"the whole-cloth dismissal of psychologic forces in the pathobiology of TS was a strategic error"*. Questions remain about whether co-occurring (co-morbid) conditions, most notably attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), should be part of the core definition, and why sensory phenomena, which are a core part of TS, are not part of the diagnostic criteria.

Who has TS?

Older estimates of the prevalence rates of TS came from tertiary referral samples, i.e., 'the sickest of the sick'. However, dropping the 'impairment criterion' from the diagnosis resulted in higher estimates of those rates, casting the condition in an entirely new light and calling for new biological models and new approaches to addressing a more common disorder.

What causes TS?

Since 1825 when French physician, Jean-Marc Gaspard Itard, related the symptoms of TS, we still do not know the cause(s) of that disease (see Fymat 2023b, Article II in this series, and Fymat 2023d). Discovering the causes of TS may help resolve the questions of what it is and who has it. Past research has been affected by the problem of referred samples, which may not reflect broader populations of persons. Further, the autosomal dominant inheritance model advanced in 2013-15 has not been validated (see Fymat 2023b and d). In addition, the PANDAS (Neuropsychiatric Disorders Associated with Streptococcal infections) hypothesis has sparked disagreement.

How should TS be studied?

TS patients are often recruited from sources that introduce ascertainment bias towards one 'type' of TS. Expanding criteria for the diagnosis, and increasing awareness of the impact of co-morbid diagnoses, has resulted in further questions of how to study TS. Developing and applying standardized instruments, along with a greater awareness of ascertainment bias in recruitment sources, will be important in genetic studies. We do not know if "we lose both signals and are just adding noise to the experimental outcome" when co-morbid conditions, such as ADHD or OCD, are included or excluded from study samples, or samples include/exclude children or adults, or patients with severe symptoms.

How should TS be (medically) treated?

People with TS face significant challenges learning about current research, especially given the rarity of the disease. Moreover, patients often need extra help locating further support resources. For them, research is a priority as it leads to a better understanding of their disease, quicker and more accurate diagnosis, innovative treatments and cures, and better health care. It represents hope for the millions of people living with TS or other rare disease(s) and their families.

While improvements have been made in the past decades with dedicated public funding and coordinated actions, rare disease research faces political and practical obstacles such as inadequate funding, small patient populations for clinical trials, and a lack of coordinated resources for patient registries. This translates into insufficient knowledge of these diseases and delays in both the diagnosis and the development of

much-needed treatments.

Research on rare diseases covers a whole spectrum – from basic research (understanding of disease mechanisms in laboratories), to pre-clinical (development of disease models, including animal and cell-based systems to test potential therapies), to translation (how to make research results translate into real benefits for patients), to clinical trials. Scientific advancements in rare disease research also contribute to progress for more common diseases and the health outcomes of individuals.

Rare diseases research in the U.S.

From the:

National Center for Advancing Translational Sciences (NCATS)

- **Rare Diseases Clinical Research Network (RDCN):** This program is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment, and data sharing. Through the RDCRN consortia, physician-scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation.

- **Gene Therapy and Gene Editing Programs - The Accelerating Medicines Partnership® Bespoke Gene Therapy Consortium (BGTC):** This program is part of the Accelerating Medicines Partnership® (AMP®) program, a public–private partnership among the National Institutes of Health (NIH), Food & Drug Administration (FDA), multiple pharmaceutical and life sciences companies, and non-profit and other organizations. The AMP program aims to improve current models for developing diagnostics and therapies. The BGTC is establishing platforms and standards to speed the development and delivery of customized or "bespoke" gene therapies that could treat millions of people affected by rare diseases, including diseases too rare to be of commercial interest. It is the first AMP initiative focused on rare diseases and the first to focus on a therapeutic platform.

Launched in October 2021, the BGTC will generate gene therapy resources that the research community can use to streamline gene therapy development for rare disorders, making the process more efficient and less costly. One of the BGTC's goals is to improve the understanding of the basic biology of the harmless adeno associated virus (AAV), a common gene-delivery vehicle or vector, how it carries genes to the correct place in cells, how those genes get into cells, and how the newly transported genes are turned on in the target cells. This information will help improve the effectiveness of AAV gene therapies. Another important BGTC goal is to improve the efficiency of both vector manufacturing and production quality control testing by developing a standard and broadly applicable set of analytic tests that can be used to manufacture viral vectors. The BGTC clinical component aims to streamline the path from animal studies to human testing, will develop strategies for streamlining the regulatory processes for FDA approval of safe and effective gene therapies, and will also develop standardized approaches to preclinical testing (e.g., toxicology studies).

- **Therapeutics for Rare and Neglected Diseases (TRND):** This program supports preclinical development of therapeutic candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application.

- **The Genetic and Rare Diseases (GARD) Information Center:** Sources of information include the National Library of Medicine (NLM), Orphanet, Human Phenotype Ontology (HPO), patient support groups and other NIH Institutes and Centers. It offers

information on genetic and rare disorders clinical trials, It uses translational science to improve the research process to get more treatments to more people more quickly.

• **The Rare Diseases Registry Program (RaDaR):** This living website provides the rare diseases community with easily accessible guidance on how to set-up and maintain high-quality registries. A registry is a collection of information about individuals, usually focused around a specific diagnosis or condition. The goal is to enable rare diseases' patient organizations to better promote and support patient-focused research. Its content includes additional instructions, best practices, testimonials and shared resources from the rare diseases community in a phased approach.

• **Rare diseases research and resources:** NCATS is committed to using research to address the public health crisis presented by rare diseases. Speeding development of treatments for patients requires innovation in science and technology and engaging patients and their support organizations as essential partners.

National Institutes of Health (NIH)

• **NIH Blueprint for Neuroscience Research:** It aims "to accelerate transformative discoveries in brain function in health, aging, and disease" by pooling the resources and expertise of various NIH entities to confront challenges too large for any single Institute or Center. Topics have ranged from transforming our understanding of dynamic neuroimmune interactions to enhancing our fundamental knowledge of interception, supporting the development of innovative tools and technologies to monitor and manipulate biomolecular condensates, and more.

• **Grand Challenges:** Their aim is to catalyze research with the potential to transform our basic understanding of the brain and our approaches to treating brain disorders.

◦ **Human Connectome Project (HCP):** An ambitious effort to map all the connections within the human brain.

◦ **Chronic Neuropathic Pain (CNP):** Supports research to understand the changes in the nervous system that cause acute, temporary pain to become chronic.

◦ **The Blueprint Neurotherapeutics Network (BPN):** Helps small laboratories develop new drugs for nervous system disorders.

• **The BRAIN Initiative®:** A coordinated effort among public and private institutions and agencies aimed at revolutionizing our understanding of the human brain.

• **The National Institute of Neurological Disorders and Stroke (NINDS)** and other components of the National Institutes of Health (NIH)—such as the National Institute of Mental Health (NIMH), the (Eunice Kennedy Shriver) National Institute of Child Health and Human Development (NICHHD), the National Institute on Drug Abuse (NIDA), and the National Institute on Deafness and Other Communication Disorders (NIDOCD)—support research relevant to TS, either at NIH laboratories or through grants to major research institutions across the country.

More information about research on TS in NIH may be found by using NIH RePORTER, a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and resources from these projects.

Department of Health & Human Services (DHHS)

Centers for Disease Control & Prevention (CDC&P)

As another component of the DHHS, the Center for Disease Control & Prevention (CDC&P) funds

professional education programs as well as TS research.

Knowledge about TS comes from studies across numerous medical and scientific disciplines, including genetics, neuroimaging, neuropathology, clinical trials (medication and non-medication), epidemiology, neurophysiology, neuroimmunology, and descriptive/diagnostic clinical science:

• **Genetic studies:** Currently, NIH-funded scientists are conducting a variety of large-scale genetic studies involving TS. Understanding the genetics of TS genes may strengthen clinical diagnosis, improve genetic counseling, lead toward a better understanding of its causes, and provide clues for more effective therapies.

• **Neurostimulation:** NINDS-funded research is testing the effectiveness and safety of deep brain stimulation (DBS) for treating tics and co-occurring conditions, such as obsessive-compulsive behaviors, in individuals with TS who do not respond well to medications and behavioral therapy. DBS uses a surgically implanted, battery-operated medical device to deliver electrical stimulation to specific areas in the brain that control movement, which blocks the abnormal nerve signals that cause symptoms (Fymat 2023b, d).

• **Neuroimaging studies:** Advances in imaging technology and an increase in trained scientists have led to an increasing use of novel and powerful techniques to identify brain regions, circuitry, and neurochemical factors important in TS and related conditions, such as ADHD and OCD.

• **Neuropathology (the study of nervous system diseases):** There has been an increase in the number and quality of donated brains from people with TS available for research. This increase, coupled with advances in neuropathological techniques, has led to initial findings with implications for neuroimaging studies and animal models of TS.

• **Clinical trials:** Recently, several clinical trials in TS have been completed or currently are underway. These include studies of stimulant treatment of ADHD in TS and behavioral treatments for reducing tic severity in children and adults. Neurostimulation treatments mentioned above such as DBS and noninvasive transcranial magnetic stimulation (TMS) in children and adults are also ongoing (Fymat 2023b, d). Smaller trials of novel approaches to treatment such as dopamine agonists and glutamatergic medications also show promise.

• **Epidemiology and clinical science:** Careful epidemiological studies (those that track the pattern or incidence of a disease) now estimate the prevalence of TS to be substantially higher than previously thought, with a wider range of severity. Also, clinical studies are providing new findings regarding TS and co-existing conditions. These include subtyping studies of TS and OCD, an examination of the link between ADHD and learning problems in children with TS, and a new appreciation of sensory tics. One of the most important and controversial areas of TS science involves the relationship between TS and autoimmune brain injury associated with group A beta-hemolytic streptococcal infections or other infectious processes. There are many epidemiological and clinical investigations currently underway in this area.

American Academy of Neurology (AAN)

AAN has an active research funding program on neurology and neurosciences.

National Organization for Rare Disorders (NORD)

The NORD Patient Registry allows patients and advocacy organizations to share experiences, so researchers better understand how to diagnose and treat rare diseases. The platform is easy-to-use, allowing patients to own their data, benefit from knowledge gained, generate clinical-grade data, and have a voice in

the design and scope of research.

Tourette Association of America (TAA)

The TAA supports a clinical database that may help identify genes involved in TS. TAA and TAA IGC have collected a database on large extended families for future studies. Novel neuroimaging studies are being employed to study tic expression and functional or cognitive deficits in TS patients. Studies of Tourette's neurophysiology and neuropathology are attempting to link deficits in TS to specific brain mechanisms, and have taken advantage of a brain bank sponsored by the TAA. Clinical trials have focused on understanding tic suppression, co-morbid conditions, novel treatment approaches such as botulinum toxin, and targeted behavioral therapies but controversy remains in the areas of deep brain stimulation and PANDAS.

Rare diseases research in Europe

In Europe, rare diseases are a priority area for research funding. Major investments have been allocated to rare disease research innovation programs and in recognition of the added-value of cross-country and multidisciplinary cooperation in this field.

Initiatives

Several initiatives have been supported to improve rare disease research including the:

• **International Rare Diseases Research Consortium (IRDRC).**

• **European Joint Program on Rare Diseases (EJPRD):** To develop an ecosystem to allow a virtuous circle between research, care, and medical innovation.

• **Past projects:** Like EPIRARE, TREAT-NMD, RD-Connect and RARE Best Practices.

• **Ongoing initiatives:** Such as the:

◦ **European Rare Diseases Registries Infrastructure (ERDRI).**

◦ **European Reference Networks.**

◦ **European research infrastructures: Such as BBMRI and ECRIN.**

◦ **Solve-RD.**

◦ **Orphanet.**

But, there is still work to be done as most rare diseases lack effective and curative treatments and unmet medical needs of people living with rare diseases are still vast.

Some limitations and needs of current research

There are numerous limitations to current research studies, including:

• **Use of self-report measures:** This can introduce bias as a result of the possible inconsistency of patients' subjective estimates. Indeed, about 50% of patients who consider themselves tic-free actually demonstrate multiple tics on videotape.

• **Need to document tic severity over time using objective measures.**

• **Need to increase sample sizes in clinical trials.**

• **Need for longitudinal follow-up duration.**

• **Need for further research on specific aspects of tic symptomatology.**

- **Need to identify reliable clinical measures:** These can be used as prognostic indicators for children with TS who present with increased tic severity at follow up.

- **Need to confirm preliminary observations regarding differences in prognosis between male and female patients with TS.**

- **Timely diagnosis of the rare cases of malignant TS: This is extremely important clinically.**

- **Need to establish the risk factors associated with malignant TS population.**

Some suggestions for future research

The following suggestions are formulated for future research in the TS disease:

Behavioral interventions for tics

This research should include comparisons of the relative efficacy of comprehensive behavioral intervention therapy (CBIT) vs pharmacotherapy.

Treatment sequencing and decision-making

Additional research should be conducted on treatment sequencing and decision-making and for whom particular sequences of treatment are most effective.

Efficacy of other behavioral treatments

Further research should continue to test the efficacy of other behavioral treatments, including exposure and response prevention, mindfulness-based treatments, or more global tic-related interventions. As the evidence is insufficient at present to conclude that CBIT delivered by teleconference is as effective as face-to-face treatment, further well-designed studies with adequate sample sizes are needed to establish non-inferiority. Additional work to more accurately characterize the neurocognitive and behavioral mechanism of action underlying CBIT will be necessary to enhance the overall effectiveness and inform patient–treatment matching algorithms.

Medications for tics

Future research on medications for tics should include non-inferiority trials of agents commonly used for the treatment of tics for which limited evidence from randomized controlled trials (RCTs) is available (Fymat 2023a, b).

- Antipsychotics: Agents for which evidence is promising but limited include the first-generation antipsychotic Fluphenazine. Trials are currently underway with the selective D1 antagonist Ecopipam and evidence on the efficacy of this drug is expected soon.

- Dopamine depleters: The dopamine depleters, Tetrabenazine, Deutetrabenazine, and Valbenazine act by blocking vesicular monoamine transporter type 2 (VMAT2). Although no randomized controlled trials have been published with the VMAT2 inhibitors in the treatment of tics, these drugs are increasingly used off-label. When appropriately dosed, they are generally well-tolerated but may be associated with drowsiness, depression, and parkinsonism. Although an initial phase II trial of Valbenazine did not reach the primary endpoint in adults and children with TS, this was thought to be due to under-dosing. Further and better-designed trials are currently underway with Deutetrabenazine and Valbenazine for the treatment of tics.

Drug efficacy and adverse effects

- **Medications combinations:** More long-term studies of drug efficacy and adverse effects are needed

as well as the efficacy and safety of medication combinations for severe tics resistant to mono-therapy.

- **Cannabis-based medicines:** Few studies have been performed investigating the efficacy and safety of cannabis-based medicine in children with various diseases. Recently it was reported that cannabidiol (CBD) may significantly reduce convulsive seizure frequency in children with Dravet's syndrome (DS). There is preliminary evidence that Tetrahydrocannabinol (THC) might also be effective in children for vomiting due to anti-neoplastic treatment and in treatment-resistant spasticity. There is increasing evidence that cannabis-based medicine might be effective in adults with TS. A recent press release for a single-dose study of a first-in-class small molecule inhibitor of monoacylglycerol lipase, ABX-1431, which regulates one of the key natural activators of the central cannabinoid CB1 receptor, suggests efficacy for the treatment of tics.

- **Deep brain stimulation:** Case reports and case series have comprised the majority of the outcomes data on the efficacy of DBS for TS. The goal of future research on DBS in TS should be to improve outcomes and quality of life by conducting well-designed multi-center studies, share data across centers, uncover best practices, and provide critical information to regulatory agencies that will lead to approval of DBS in TS. There are important limitations to the currently available trials using DBS in TS. The uncertainty in optimal target and the individual variability in programming and management between participants make trials challenging. Recent research on DBS in TS has revealed the intriguing possibility that it may not be necessary to have the devices activated continuously as has been the standard for other movement disorders. Moreover, adaptive closed-loop DBS is being explored in an ongoing clinical trial.

- **Lifestyle modifications:** Future research on the effect of special diets, nutritional supplements, and exercise on tic severity is needed.

Research participation and advocacy

Participation

People living with a rare disease can be directly implicated in each step of the rare disease research process. For example, they could: advocate for research when there is none by connecting with researchers working on similar diseases; help researchers design studies that reflect their needs; start or contribute to a registry so that researchers can find patients' data and participate in research activities.

Often patient organizations can support researchers to recruit patients and encourage them to donate samples to boost research.

Patient representatives can participate in the EURORDIS Open Academy on Scientific Innovation and Translational Research to become valued partners in rare disease research by developing their knowledge and capacities in this area. All EURORDIS Open Academy training courses are free and provided through a blend of e-learning courses and webinars.

Advocacy

Rare diseases are a prime example of a research area that can strongly benefit from coordination and collaboration on a national, European, and international scale.

The patient community in Europe, supported by EURORDIS, has effectively advocated for increased European cooperation in research on rare diseases. In turn, EURORDIS has also promoted the need for rare disease research and budgeting as a priority at the national level, in particular through rare disease national plans.

As a result, funding opportunities for research have increased in recent decades. Between 2007 and 2017 the European Commission (EC) invested over 874 M€ in research on rare diseases. The EU Orphan Drug Regulation (ODR) has also provided incentives (such as market exclusivity) that encourage companies to invest in rare disease research. However, there remains a lack of research to cover every one of the 6,000+ rare diseases.

EURORDIS promoted rare diseases as a research priority in EU research framework programs such as 'Horizon 2020' and in the upcoming 'Horizon Europe 2021-2027', and played an instrumental role in the creation of the:

• **International Rare Diseases Research Consortium (IRDiRC).**

• **European Joint Program on Rare Diseases (EJPRD).**

• **European Reference Networks (ERN).**

• **EURORDIS Position Paper on Rare Disease Research:** It set out the ethical, social, economic, and scientific grounds of rare disease research, and shaped research priorities.

Summary and conclusions

The inherently changing nature of the core symptoms of TS complicates research design, resulting in questions about medications in clinical practice. Compared to the progress made in gene discovery in certain neurodevelopmental or mental health disorders, the scale of related TS research is lagging. The TS research landscape can be divided into five broad questions: What is it? Who has it? What causes it? How should it be studied? and How should it be (medically) treated? While improvements have been made in the past decades with dedicated public funding and coordinated actions, rare disease research faces political and practical obstacles. Rare disease research in the U.S.and in Europe has been detailed in great lengths.Some limitations and needs of current research as welt as suggestions for research have been made, including behavioral interventions for tics, treatment sequencing and decision-making, efficacy of other behavioral treatments, medications for tics, and drug efficacy and adverse effects.

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