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ADVANCED IN THE DIAGNOSIS AND TREATMENT OF MOVEMENT DISORDERS PRESENTING AS TICS

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Tic disorders are pathological conditions that have recently seen a sharp rise in prevalence and require careful attention regarding diagnosis, differential diagnosis, treatment, and monitoring—particularly given that most of them onset during childhood. This underscores the relevance of the topic and necessitates the implementation of updated domestic regulations and guidelines, as well as familiarity with international recommendations, while considering the etiological and pathophysiological characteristics underlying the development of this pathology [1–4].

The prevalence of tic disorders is estimated at approximately 0.5-1% of the general population, with a marked male predominance (the male-to-female ratio ranges from 3:1 to 4:1) [5,6]. The typical age of onset is between 6 and 8 years, and symptoms often follow a waxing and waning course, fluctuating in frequency, intensity, and complexity over time [2,3].

Comorbid conditions are common and include attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and mood disorders; ADHD is diagnosed in a significant proportion of patients, while anxiety and mood disorders affect approximately one-third of individuals [3,4]. OCD is also a major comorbid condition, with reported prevalence rates ranging from 20% to 60%. These comorbidities often lead to lifelong impairments in adaptive functioning and significantly impact quality of life. The clinical spectrum of tic disorders encompasses a range of symptoms and associated conditions [4-6].

The aim of this study is to provide an overview of the classification of tic disorders in accordance with the European guidelines for the diagnosis and pharmacological treatment of tic disorders and Tourette syndrome.

Tics are brief, sudden, involuntary, non-rhythmic, repetitive, and stereotyped movements or sounds that may occur intermittently or continuously [7].

Tic disorders are classified as neurodevelopmental disorders:

307.21 Provisional tic disorder – Motor and/or vocal tics lasting for less than 1 year.

307.22 Chronic motor or vocal tic disorder – Motor or vocal tics (but not both), lasting for more than 1 year.

307.23 Tourette's Disorder – Presence of multiple motor tics and at least one vocal tic, lasting for more than one year.

307.20 Other (specified) tic disorder – Symptoms do not fully meet the criteria for a specific disorder.

307.20 Unspecified tic disorder: Insufficient information for a precise diagnosis [7].

Tic disorders have a strong genetic basis, with heritability estimates ranging from 0.58 to 0.77, as confirmed by twin studies. Concordance rates are significantly higher in monozygotic twins than in dizygotic twins. First-degree relatives face a risk of developing the disorder that is tens of times higher [9,10]. The genetic risk is polygenic and involves the genes SLITRK1, HDC, CNTNAP2, NRXN1, and CNTN6.

Environmental risk factors for the development of tic disorders include prenatal and perinatal complications – such as maternal smoking, low birth weight, and maternal stress – as well as obstetric factors like impaired fetal growth, preterm birth, breech presentation, and Caesarean section. Early-life infections, particularly Group A streptococcal infections, have been investigated for their role in tic disorders; however, the hypothesis regarding Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) remains controversial due to conflicting evidence regarding a causal link. Immune system activation and inflammation have been associated with the pathogenesis and clinical course of tic disorders. [11,12]

A comprehensive assessment of both children and adults includes evaluating the most distressing complaints and symptoms, assessing the progression of symptoms, and inquiring about potential stressors and triggers. In the case of children and adolescents specifically, a developmental history is obtained, and family functioning is assessed – including parenting styles, parental conflict, social support networks, and financial and housing situations. For adults, relationship status, current employment, and financial or housing circumstances are also evaluated. Additionally, where available, information regarding tics, OCD, family history of ADHD, and the patient's medical status is gathered from parents, partners, or caregivers close to the patient [1, 13,14].

Tic disorders are characterized by sudden, rapid, repetitive, non-rhythmic, and involuntary movements or vocalizations, which can be simple or complex [8]. Simple motor tics involve repetitive movements of specific muscle groups—such as eye blinking, neck jerking, or shoulder shrugging – whereas complex motor tics consist of coordinated movements involving multiple muscle groups, such as repetitive grooming behaviors or deep knee bending. Simple vocal tics are non-verbal sounds like throat-clearing or grunting, while complex vocal tics involve intelligible words and can – though rarely – manifest as coprolalia, the repetitive vocalization of obscenities. Tics often intensify during stress and may improve during activities requiring moderate physical or mental engagement. They can usually be suppressed for short periods; however, suppression may lead to discomfort or heightened premonitory urges – unpleasant sensations or mental impulses that are relieved by performing the tic.

Although tics are generally considered involuntary movements, they are often associated with a temporary ability to suppress them. [2,15,16]

The frequency, rate, and intensity of tics fluctuate over time, exhibiting a waxing and waning pattern. Tics are often preceded by premonitory urges – uncomfortable physical sensations or mental impulses that are relieved by the tic. The DSM-5 defines a provisional tic as a motor and/or vocal tic present for less than one year following onset, with an onset before the age of 18. A chronic motor or vocal tic requires the presence of either a motor or a vocal tic (but not both) for more than one year, with an onset before the age of 18. Tourette syndrome is diagnosed based on the presence of multiple motor tics and at least one vocal tic – not necessarily occurring simultaneously – persisting for more than one year, with an onset before the age of 18 [7,8].

The Movement Disorder Society recommends five scales for assessing tics – including severity, impairment, and premonitory urges: the Yale Global Tic Severity Scale (YGTSS), the Clinical Global Impression for Tourette Syndrome (TS-CGI), the Tourette Disorder Scale (TDS), the Shapiro-Tourette Syndrome Severity Scale (STSSS), the Premonitory Urge for Tics Scale (PUTS), and the Premonitory Urge for Tic Disorders Scale-Revised (PUTS-R). Six other scales were rated as "recommended": the Rush Video-Based Tic Rating Scale (RVTRS), the Motor Tic, Obsession and Compulsion, Vocal Tic Evaluation Survey (MOVES), the Tourette Syndrome Global Scale (TSGS), the Global Tic Rating Scale (GTRS), the Parental Tic Questionnaire (PTQ), and the Tourette Syndrome Symptom List (TSSL) [1,2,17,18].

The Yale Global Tic Severity Scale (YGTSS) remains the gold standard for assessing tics.

Thorough physical and neurological examinations are performed—particularly when clinically indicated—to rule out other neurological disorders alongside tics. Additional diagnostic procedures, such as electroencephalography (EEG), are conducted to exclude other potential conditions that could cause similar symptoms, such as focal epilepsy. Magnetic resonance imaging (MRI) is used if an organic brain lesion is suspected [19-22].

In 2022, the European Society for the Study of Tourette Syndrome (ESSTS) published an update to the pharmacological treatment section of the European guidelines on Tourette syndrome and tic disorders, based on a review of recent literature with a particular focus on other evidence-based guidelines, meta-analyses, and randomized double-blind studies.

Behavioral therapies are considered first-line treatments for tic disorders, with Habit Reversal Training (HRT) and Comprehensive Behavioral Intervention for Tics (CBIT) having demonstrated efficacy in randomized controlled trials and meta-analyses. [4,23-26]

Pharmacological treatment should be considered when behavioral interventions are ineffective or unavailable (e.g., lack of access to behavioral therapy—including cost-related issues—or patient factors such as age, cognitive function, or willingness to participate), or when patients exhibit severe, aggressive tics requiring immediate treatment [27,28].

Tourette syndrome and other tic disorders are associated with dysfunction in multiple neurotransmitter systems, particularly the dopaminergic system. Dopamine receptor antagonists have the strongest empirical support but are often limited by side effects [2].

A survey by the European Society for the Study of Tourette Syndrome (ESSTS) indicates that aripiprazole, an atypical antipsychotic, is currently the most widely used pharmacological treatment for Tourette syndrome across both age groups (children/adolescents and adults). This may be attributed to several factors, including its unique pharmacological profile as a partial dopamine agonist [40] and the availability of several randomized controlled trials (RCTs) with sufficient sample sizes demonstrating a favorable benefit-risk ratio, largely due to its positive side-effect profile [30,31]. Tiapride—the second most frequently prescribed medication for children and adolescents with tics, particularly in Germany—shares a similar mechanism of action with aripiprazole, showing a maximum dopamine receptor occupancy of 80% even at excessive concentrations. Another atypical antipsychotic is risperidone; while supported by a strong evidence base, it is associated with weight gain and metabolic side effects [32,33].

Typical antipsychotics, such as haloperidol, despite their proven efficacy and official registration in Europe, are used less frequently due to an unfavorable side-effect profile [4,34].

In addition to dopaminergic system dysfunction, imbalances exist in other neurotransmitter systems, including the serotonergic, noradrenergic, glutamatergic, GABAergic, cholinergic, histaminergic, endocannabinoid, and opioid systems [2, 35,36]. These findings provide a rationale for using agents other than dopamine-blocking drugs, particularly for treating tics that are resistant to dopamine-modulating agents. A European survey documented that noradrenergic drugs—specifically alpha-2-adrenergic agonists (clonidine, guanfacine)—are the third most frequently used medications when both age groups are considered together. Notably, while noradrenergic drugs show low efficacy in patients with tics alone, their effectiveness increases significantly in patients (especially children and adolescents) with co-occurring tics and ADHD, regarding the reduction of both tics and ADHD symptoms [37,38].

In treatment-resistant cases, one might consider medications for which the evidence base is sometimes still limited and which are less frequently prescribed by ESSTS experts. Reasonable choices include antipsychotics—specifically haloperidol, pimozide, quetiapine, sulpiride, and amisulpride—as well as cannabis-based medications, topiramate, and botulinum toxin injections [4,36,37]. Among these agents, topiramate has demonstrated the best results. In 2020, a meta-analysis was published evaluating the efficacy and tolerability of topiramate for tic disorders in children compared to haloperidol and tiapride [22]. In total, the meta-analysis included 15 studies involving 1,070 participants aged 2 to 17 years (693 [64.71%] male), with 14 of these studies assessing the efficacy of topiramate for treating tic disorders. The results indicated that topiramate was more effective than the control medications (RR: 1.13, 95% confidence interval: [1.06–1.20], I^2=36%, Q = 20.31, p = 0.09). Regarding

side effects, 15 studies were included in the meta-analysis, and the results showed that topiramate was associated with fewer side effects than the control drugs (RR: 0.54, 95% confidence interval: [0.46–0.65], $I^2 = 45\%$, $Q = 25.49$, $p = 0.03$). It was concluded that, compared to haloperidol and tiapride, topiramate appears to be a promising drug with good efficacy and tolerability in children with tic disorders. Topiramate is also a potential treatment of choice for patients with tics who have obesity or OCD. [22]

The decision to prescribe a specific treatment is an individual choice made by the clinician in collaboration with the patient and their family, depending on the patient's needs, preferences, and priorities, as well as the physician's preferences, experience, and local regulatory requirements [38-40]. In general, drug titration following the "start low, go slow" principle is recommended; this means therapy should begin with the lowest possible dose and be increased gradually. It is important to remember that the doses of antipsychotic medications typically used to treat tics are significantly lower than those used for psychotic disorders [41,42]. Depending on its individual receptor-binding profile, each drug carries a risk of specific side effects [43, 44]. Therefore, when selecting the most suitable medication for a patient, one must consider not only efficacy but also the potential side effects of each drug, and careful monitoring for side effects is recommended [55, 56]. When discontinuing treatment, a gradual reduction of the antipsychotic dose is recommended to avoid withdrawal-related dyskinesia [45-48].

In general, the emphasis is placed on individualized, multimodal treatment plans that combine behavioral and pharmacological strategies [4,49].

Conclusion. Tic disorders constitute a complex group of pathological conditions with a multifactorial etiology involving genetic, neurobiological, and pathophysiological factors. Cortico-striato-thalamo-cortical circuits and neurotransmitter imbalances—particularly involving dopamine and gamma-aminobutyric acid—underlie the pathophysiology of these disorders. The clinical presentation is heterogeneous; tics vary in type, frequency, and severity and are frequently accompanied by comorbid neurological and neuropsychiatric conditions, such as attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. Diagnosis remains clinical, based on a detailed medical history and examination, as there are currently no definitive biomarkers.

Therapeutic approaches prioritize behavioral interventions targeting premonitory urges and tic-suppression mechanisms. Pharmacological treatments—primarily dopamine receptor antagonists and alpha-2 adrenergic receptor agonists—provide symptom relief, though their use requires balancing benefits against potential side effects. Among other medications, topiramate stands out as a particularly promising option. Ongoing research into neurobiological mechanisms and novel therapeutic targets continues to advance the understanding and treatment of tic disorders, with the aim of improving patients' quality of life.

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