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SPECIAL REPORT

When is pharmacotherapy necessary for Tourette syndrome? The risks vs reward

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ABSTRACT

Introduction: Tourette syndrome is a neurodevelopmental disorder characterized by chronic motor and vocal tics. Both tic severity and co-morbid psychiatric disorders can affect patients' health-related quality of life to an extent that warrants active treatment interventions. Different decisional approaches can be implemented to determine the need for pharmacotherapy.

Areas covered: A critical appraisal of the existing literature on the clinical scenarios where pharmacotherapy for Tourette syndrome is deemed necessary has highlighted three indications: (1) physical discomfort – e.g. pain or injury; (2) emotional or social problems – e.g. depression or isolation; or (3) functional interference – e.g. impairment of academic achievements.

Expert opinion: Pharmacotherapy for tic disorders aims to reduce tic severity enough to improve daily functioning and health-related quality of life rather than to eliminate symptoms. Expert consensus emphasizes patient-centered decision-making that integrates disease-specific quality of life measures with objective tic severity scales. Medications may be prioritized when tics cause significant impairment, pose medical risks, require rapid control, or coexist with treatable co-morbidities. Current guidelines rely largely on limited trials and expert opinion, with dopamine-modulating agents and alpha-2 agonists being most commonly used. Further research should focus on open questions about real-world effectiveness and generalizability of individual pharmacological agents.

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Tics; tic disorders; Tourette syndrome; pharmacotherapy; benefits; risks

1. Introduction

Tics are defined as sudden, repetitive, non-rhythmic movements (motor tics) or vocalizations (vocal tics). Subjectively, they are often described as voluntary responses to overwhelming internal sensations, known as premonitory urges [1,2]. This peculiar feature of tics has led to their characterization as 'unvoluntary' movements or vocalizations: behaviors that are neither fully involuntary nor fully voluntary [3]. Tourette syndrome is a chronic tic disorder marked by multiple motor tics and at least one vocal tic, with onset occurring before the age of 18. Its prevalence is estimated at roughly 0.5–0.8%, with males affected three to four times more frequently than females. Most patients initially present with simple twitching, jerking movements affecting the face and neck, followed by simple sounds like sniffing, grunting, coughing, or throat clearing. Complex motor tics involve coordinated actions across several muscle groups, and complex vocal tics consist of full words or phrases, including repeated words (palilalia), imitation of others' speech (echolalia), and, less commonly, involuntary utterance of obscene words (coprolalia). Despite its frequent mention in association with Tourette syndrome, coprolalia is reported by about 10% of patients in the general community – up to 30% in specialist clinics [4]. Approximately 90% of individuals with Tourette syndrome also experience co-occurring behavioral or psychiatric conditions, including obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, impulsivity, anxiety, and depression [1,2]. The multifaceted neuropsychiatric spectrum of Tourette syndrome is often the reason for referral to specialist services, as health-related quality of life can be affected more severely the psychiatric co-morbidities than by tic severity [1,2]. Tic-related obsessive-compulsive behaviors – reported by up to 70% of patients – include repetitive counting (arithmomania), checking, ordering, forced touching, and a strong need for symmetry or 'just right' sensations. These overlaps in symptoms likely reflect shared underlying neurobiological mechanisms, which have important implications for treatment.

Importantly, tics in the context of Tourette syndrome are chronic, and their persistence over at least 12 months prompt a diagnostic revision from provisional tic disorder to Tourette syndrome. Individuals who have chronic motor or vocal tics (but not both) are diagnosed with persistent motor/vocal tic disorder. Cases of secondary tourettism are relatively rare and present with tics that arise as a consequence of an identifiable, acquired, or exogenous cause, rather than representing a primary neurodevelopmental process. Although the precise pathophysiology of Tourette syndrome remains unclear, abnormalities within the cortico-striato-thalamo-cortical circuits and disruptions in

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Article highlights

- Different decisional approaches can determine the need for pharmacotherapy in patients with Tourette syndrome (TS).
- Indications for pharmacotherapy in TS include physical discomfort, emotional/social problems, functional interference.
- Objective tic severity scales should be integrated by disease-specific quality of life measures.
- Medications should be prioritized for severe tics posing medical risks and requiring rapid control.
- Dopamine-modulating agents and alpha-2 agonists are the most commonly used pharmacotherapy in patients with TS.

sensorimotor processing appear central [5]. Multiple neurotransmitter systems beyond dopaminergic pathways are thought to contribute. The role of impaired inhibitory control remains debated. Given the typical course of tic disorders, some children newly diagnosed with Tourette syndrome may not need active treatment initially and may benefit more from psychoeducation and careful monitoring. For those requiring intervention, treatment options include behavioral therapies – externally focused attention strategies and structured interventions, such as habit reversal training and exposure and response prevention – and pharmacotherapy [5–8]. More invasive approaches, including deep brain stimulation, are reserved for severe, treatment-resistant cases. Finally, the use of complementary and alternative medicines is widespread but lacking in scientific evidence [9].

The pharmacologic options for Tourette syndrome range from first- and second-generation antidopaminergic agents and alpha-2 agonists to several other medications with less robust evidence, including monoamine-depleting agents, anticonvulsants, cannabinoids, and traditional Chinese therapies. The different classes of medications are characterized by different efficacy and tolerability profiles, and any decisions regarding the choice of first, second and third-line pharmacological agents should be guided by the patient's clinical presentation, as well as their individual needs and circumstances. While only three medications have been granted approval by the United States Food and Drug Administration (Haloperidol, Pimozide, Aripiprazole), evidence-based guidelines for pharmacotherapy have been updated in recent years, with major publications from the American Academy of Neurology (AAN) in 2019 [10] and the European Society for the Study of Tourette Syndrome (ESSTS) in 2022 [11]. The characteristics of the most commonly used pharmacotherapy agents for the treatment of tics in patients with Tourette syndrome are summarized in Table 1, together with their respective recommendation levels according to the updated AAN and ESSTS guidelines.

2. Indications for pharmacotherapy in Tourette syndrome

Treatment decisions for Tourette syndrome should be grounded in a comprehensive and wide-ranging diagnostic assessment [12]. In addition to quantifying problems induced by tics, it is essential to search for an etiology (e.g. physiological/neurodevelopmental tics *versus* functional tic-like behaviors), to optimize diagnostic accuracy and achieve more targeted and effective treatment interventions [13]. Clinically, medications tend to produce benefits more quickly than behavioral therapies. However, establishing universal guidelines for when to initiate pharmacologic treatment is challenging for several reasons: symptoms vary greatly between individuals, tics naturally fluctuate over time, and coexisting conditions can influence how well treatments work. Additionally, a person's subjective level of distress does not always align with the observed severity of tics: some individuals with pronounced tics experience little impairment, while others with mild tics may suffer considerably.

Many children and adolescents with Tourette syndrome do not need active treatment for their tics because the symptoms do not disrupt daily functioning or subjective wellbeing to a significant extent. In fact, it is widely known that only a small portion of individuals with tics seek clinical care. After receiving psychoeducation and reassurance, many patients do well with a watch-and-wait approach. The goal of psychoeducation in Tourette syndrome is to help individuals better tolerate their symptoms and reduce stress. It typically includes information about the short- and long-term variability of tics, the expected clinical course, and possible co-morbid conditions. A watchful waiting strategy is further supported by the current lack of evidence regarding how pharmacological treatments affect the long-term natural course of Tourette syndrome or influence brain development. As a result, available medications provide only symptomatic relief – they typically lessen tics but do not cure them. Pharmacologic treatments should be considered, in addition to psychoeducation, for individuals who clearly experience impairment from their tics – either at the initial evaluation or later if symptoms worsen. It has been recommended that pharmacotherapy should be considered in different circumstances listed below, especially when persisting for some days [14].

2.1. Tics cause physical discomfort (e.g. pain or injury)

Pain in Tourette syndrome can result directly from performing frequent or forceful tics, especially when these involve sudden or repetitive extreme movements of areas like the head or neck. This pain is most often musculoskeletal, though neuropathic pain has occasionally been reported. Injuries may also occur when a limb or other body part is struck or strikes an object during large-amplitude tics, and such incidents can sometimes be difficult to distinguish from intentional self-harm. In addition, some individuals find that experiencing pain temporarily reduces their tics, leading them in some cases to deliberately induce pain for relief. A smaller group of patients reports pain linked to the compelling urge to tic or to the intensification of premonitory urges during attempts to voluntarily suppress their tics. Others note that tics can exacerbate existing headaches or migraines. In these situations, tic-suppressing medications may lessen the need for pain treatments and should be considered.

2.2. Tics cause emotional or social problems for the patient (e.g. depression or isolation)

A considerable proportion of patients with Tourette syndrome develop anxiety and affective symptoms, with low self-esteem, and/or social withdrawal. Persistent complex motor tics and loud vocal tics can lead to significant social difficulties. Tics may contribute to isolation, bullying, or stigmatization, and

Table 1. Characteristics of the most commonly used pharmacotherapy agents for the treatment of tics in patients with Tourette syndrome.

Pharmacological class	Main mechanism(s) of action	Pharmacological agent	Main (dose-dependent) adverse effect(s)	Recommendation level (AAN 2019/ESSTS 2022)
First-generation antidopaminergics	Dopamine D2 receptor antagonism	Haloperidol	Sedation, parkinsonism	Level A – probably effective, FDA-approved (AAN)/ 2nd line due to tolerability (ESSTS)
		Pimozide	Sedation, QT prolongation	Level A – possibly effective, FDA-approved (AAN)/ 2nd line due to tolerability (ESSTS)
Second-generation antidopaminergics	Dopamine D2 and serotonin 5-HT2A receptor antagonism	Risperidone	Sedation, weight gain, hyperprolactinemia	Level B – probably effective (AAN)/ 1st line (ESSTS)
Third-generation antidopaminergics	Partial dopamine D2 receptor agonism	Aripiprazole	Akathisia, nausea, insomnia	Level B – probably effective, FDA-approved (AAN)/ 1st line (ESSTS)
Alpha-2 adrenergic agonists	Presynaptic alpha-2A-receptor agonism	Clonidine	Sedation, hypotension	Level B – probably effective, esp. with co-morbid ADHD (AAN)/ 1st line – esp. with co-morbid ADHD (ESSTS)
		Guanfacine	Sedation, hypotension	Level B – possibly effective, esp. with co-morbid ADHD (AAN)/ 1st line – esp. with co-morbid ADHD (ESSTS)
VMAT2 inhibitors	Blockade of monoamine transporter 2	Tetrabenazine	Sedation, depression, parkinsonism	Insufficient evidence (AAN)/ 3rd line (ESSTS)
Anticonvulsants	Potentiation of GABA-A receptor-mediated inhibition, blockade of AMPA/kainate glutamate receptors	Topiramate	Cognitive changes, weight loss, paresthesia	Level B – possibly effective (AAN)/ 2nd line (ESSTS)

Abbreviations. AAN, American Academy of Neurology; ADHD, attention-deficit/hyperactivity disorder; ESSTS, European Society for the Study of Tourette Syndrome; FDA, Food and Drug Administration.

loud vocalizations can even result in a child being removed from the classroom. In such situations, reducing tic severity – along with providing psychoeducation to teachers – can be highly beneficial. However, tics do not always cause social impairment, so each case must be evaluated carefully. For instance, parents of younger children may be overly concerned about potential social problems, while adolescents sometimes overestimate how negatively their peers view their tics. In early elementary school, classmates are often relatively accepting. When social isolation occurs at this age, it is more commonly driven by co-morbid conditions than by tics themselves. In older grades, however, bullying and stigmatization related to tics tend to become more frequent. With appropriate psychoeducation, many children and adolescents learn to accept their symptoms and wait for natural improvement. Nonetheless, pharmacotherapy may be appropriate in some cases to help prevent or reduce social stigmatization.

2.3. *Tics cause functional interference (e.g. impairment of academic achievements)*

Functional interference has been reported to occur at multiple levels. Homework can be affected by bouts of tics. Sleep may be disturbed because of initial insomnia and/or fragmented sleep pattern, resulting in decreased arousal during daytime. Frequent vocal tics can disrupt speech fluency and make conversations more difficult. Additionally, children may devote considerable mental effort to suppressing their tics in the classroom, which can reduce their ability to concentrate on schoolwork. Finally, both attentional deficits and time-consuming tic-related obsessive-compulsive rituals negatively affect academic performance.

3. Expert opinion

The aim of pharmacologic treatment for tic disorders is not to completely eradicate tics, but to lessen their frequency and intensity so that individuals can function more effectively and experience a better health-related quality of life. Although medications can reduce tic symptoms, they are not considered curative. Quality of life measures specific to Tourette syndrome serve as valuable indicators for when pharmacotherapy may be needed, as they capture the real-life impact of symptoms rather than merely quantifying tic frequency [15]. Tools such as the Gilles de la Tourette Syndrome – Quality of Life scale (GTS-QoL) help clinicians assess subjective experiences and functional limitations, offering insights that generic assessments may overlook [16,17]. These instruments support a patient-centered approach by ensuring that treatment aligns with the individual's most important concerns. Thus, if a patient shows significant impairment in a particular quality of life domain – even when overall tic severity appears moderate – medication may be warranted to restore functioning and well-being [Figure 1]. Moreover, the use of disease-specific quality of life measures should be integrated by the routine use of objective tic severity rating scales such as the Yale Global Tic Severity Scale [18]: for instance, pharmacotherapy might have to be prioritized in cases with marked tic severity associated with self-injurious or aggressive behaviors,

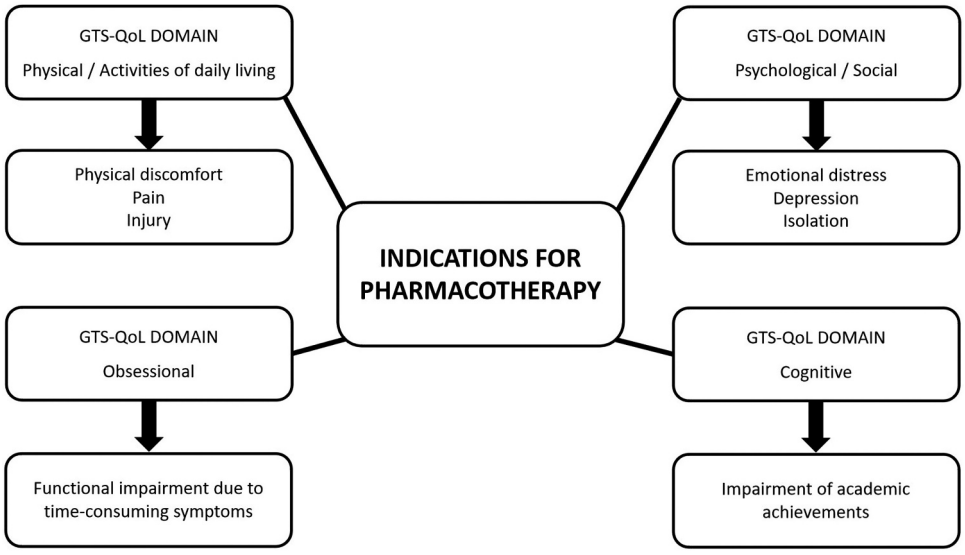

Figure 1. Domains of the Gilles de la Tourette syndrome – Quality of Life (GTS-QoL) scale and possible indications for pharmacotherapy in Tourette syndrome.

potentially resulting in profound functional impairment, medical complications, and/or life-threatening consequences (so-called malignant Tourette syndrome) [19].

The results of a randomized controlled trial comparing behavioral, educational, and pharmacological treatments in youths with Tourette syndrome or other chronic tic disorders showed that behavioral therapy and medications are similarly effective for reducing tic severity [20]. Behavioral therapy approaches such as habit reversal training and exposure and response prevention are not always locally accessible or indeed feasible because of the characteristics of the individual patient – including developmental stage, introspective skills, and subjective motivation among other factors. There are a number of situations when pharmacological treatment should be considered as a first-line treatment approach: typically, when there is a subjective preference for pharmacotherapy, when tics are severe or significantly impairing health-related quality of life and a rapid tic reduction is urgently required, and when there is co-morbidity that may also benefit from medication. For example, patients with tics and co-morbid attention-deficit /hyperactivity disorder might benefit from the prescription of an alpha-2 agonist for both conditions. Based on the available evidence, it is possible to propose a flowchart for rational pharmacotherapy in patients with Tourette syndrome [Figure 2].

In summary, pharmacologic treatment plays a critical role in managing Tourette syndrome. Current recommended options for tic reduction feature several medications used off-label. Treatment guidelines – including the recent ESSTS and AAN Clinical Guidelines – are based largely on small placebo-controlled trials, additional non-placebo-controlled studies, case series, and expert opinion [21]. Dopamine-modulating medications and alpha-2 agonists remain the most frequently

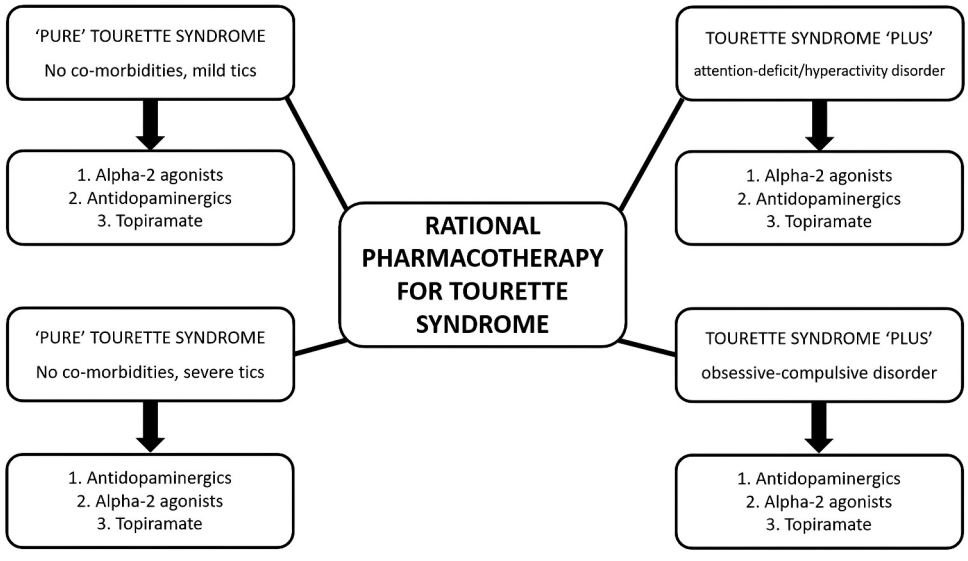

Figure 2. Flowchart for rational pharmacotherapy in patients with Tourette syndrome.

prescribed agents [22]. Although newer treatments targeting mechanisms such as glutamatergic or endocannabinoid pathways have been explored, findings are still preliminary [23]. It is also important to recognize that most historical research has focused on young white males, which may restrict the generalizability of findings, and that long-term outcome data for common pharmacologic treatments remain scarce. The same applies to the characterization of the tolerability profiles of the most commonly used pharmacological agents, such as second- and third-generation antidopaminergic medications [24]. Validation of the usefulness of instruments such as the GTS-QoL in determining the pharmacotherapy of choice for an individual patient is an area that requires further study. Future clinical research should clarify the tolerability-versus-benefit ratio of tic pharmacotherapy by conducting long-term, diverse-population studies that assess real-world effectiveness, side-effect burden, and patient-centered outcomes, ultimately guiding more precise, individualized treatment decisions.

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