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Practice guidelines

French guidelines for the diagnosis and management of Tourette syndrome☆

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https://doi.org/10.1016/j.neurol.2024.04.005

Please cite this article in press as: Hartmann A, et al. French guidelines for the diagnosis and management of Tourette syndrome. Revue neurologique (2024), https://doi.org/10.1016/j.neurol.2024.04.005

INFO ARTICLE

Article history:
Received 5 February 2024
Received in revised form
22 March 2024
Accepted 9 April 2024
Available online xxx

Keywords:
Tics
Tourette syndrome
Guidelines

ABSTRACT

The term ''Gilles de la Tourette syndrome'', or the more commonly used term ''Tourette syndrome'' (TS) refers to the association of motor and phonic tics which evolve in a context of variable but frequent psychiatric comorbidity. The syndrome is characterized by the association of several motor tics and at least one phonic tic that have no identifiable cause, are present for at least one year and appear before the age of 18. The presence of coprolalia is not necessary to establish or rule out the diagnosis, as it is present in only 10% of cases. The diagnosis of TS is purely clinical and is based on the symptoms defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). No additional tests are required to confirm the diagnosis of TS. However, to exclude certain differential diagnoses, further tests may be necessary. Very frequently, one or more psychiatric comorbidities are also present, including attention deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety, explosive outbursts, self-injurious behaviors, learning disorders or autism spectrum disorder. The condition begins in childhood around 6 or 7 years of age and progresses gradually, with periods of relative waxing and waning of tics. The majority of patients experience improvement by the end of the second decade of life, but symptoms may persist into adulthood in around one-third of patients. The cause of TS is unknown, but genetic susceptibility and certain environmental factors appear to play a role. The treatment of TS and severe forms of tics is often challenging and requires a multidisciplinary approach (involving the general practitioner (GP), pediatrician, psychiatrist, neurologist, school or occupational physicians, psychologist and social workers). In mild forms, education (of young patients, parents and siblings) and psychological management are usually recommended. Medical treatments, including antipsychotics, are essential in the moderate to severe forms of the disease (i.e. when there is a functional and/or psychosocial discomfort linked to tics). Over the past decade, cognitive-behavioral therapies have been validated for the treatment of tics. For certain isolated tics, botulinum toxin injections may also be useful. Psychiatric comorbidities, when present, often require a specific treatment. For very severe forms of TS, treatment by deep brain stimulation offers real therapeutic hope. If tics are suspected and social or functional impairment is significant, specialist advice should be sought, in accordance with the patient's age (psychiatrist/child psychiatrist; neurologist/pediatric neurologist). They will determine tic severity and the presence or absence of comorbidities. The GP will take over the management and prescription of treatment: encouraging treatment compliance, assessing side effects, and combating stigmatization among family and friends. They will also play an important role in rehabilitation therapies, as well as in ensuring that accommodations are made in the patient's schooling or professional environment.

1. Introduction

The term ''Tourette syndrome'' (TS) refers to the association of motor and phonic tics with frequently occurring but varying degrees of psychiatric comorbidities.

Specifically, TS is characterized by the association of several motor tics and at least one phonic tic that are present for at least one year and appear before the age of 18. The diagnosis of TS is clinical and is based on the symptoms defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, see Online supplement Annex 1).

Psychiatric comorbidities are also very common, and may include attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, explosive outbursts, self-injurious behaviors, learning disorders or autism spectrum disorder [1]. The condition begins in childhood, and evolves through a succession of periods of relative waxing and waning of tics. Improvement is observed by the end of the second decade of life in the majority of patients, but relevant symptoms may persist into adulthood in approximately one-third of patients [2].

The cause of TS is unknown, but genetic susceptibility and environmental factors appear to play a role.

The prevalence of TS is estimated at 0.5–1% of school-aged children, but this figure does not determine the percentage of people requiring medical follow-up [3]. Also, precise numbers for the adult population are not available at present.

Please cite this article in press as: Hartmann A, et al. French guidelines for the diagnosis and management of Tourette syndrome. Revue neurologique (2024), https://doi.org/10.1016/j.neurol.2024.04.005

The treatment of TS and severe forms of tics is often difficult and requires a multidisciplinary approach (including psychiatrists, neurologists, psychologists and social workers). In mild forms, education and psychological management are usually recommended. Medical treatments, including antipsychotics, are essential in the moderate to severe forms of the disease and they should be initiated as soon as necessary. Over the past decade, cognitive-behavioural therapies have been validated for the treatment of tics. For certain isolated tics, botulinum toxin injections may also be useful. Psychiatric comorbidities, when present, often require specific treatments. For very severe forms of TS, treatment with deep brain stimulation offers real therapeutic hope but long term follow up results of these patients are not available at present, so caution needs to exercised [4,5].

2. Objectives of the National Diagnostic and Care Protocol

The objective of this French guidelines for the diagnosis and management (*Protocole national de diagnostic et de soins; PNDS*) is to inform healthcare professionals of the current optimal diagnostic and therapeutic management as well as provide the care pathway of a patient with TS. Its aim is to optimize and harmonize the management and monitoring of this disorder. It also allows for the identification of medicinal products used for indications not covered by their Marketing Authorization (MA), as well as medications, products or services required for patient care but not usually reimbursed by health insurance.

This PNDS can be used as a reference document by the GP in order to optimize the coordination of care in consultation with the specialist.

The PNDS cannot, however, consider all specific cases, all comorbidities or complications, all therapeutic particularities or all hospital care protocols. It cannot claim to be exhaustive in terms of possible management strategies, nor does it replace the physician's individual responsibility to their patient. The protocol does however describe the current gold standard of management for a patient with TS. It must be updated as new data are validated.

This PNDS was developed in accordance with the ''method for developing a national diagnosis and care protocol for rare diseases (*méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares*)'' published by the French National Authority for Health (*Haute Autorité de santé*; HAS) in 2012 (methodological guide available on the HAS website: https://www.has-sante.fr/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds).

A more detailed document that served as the basis for preparing the PNDS, including an analysis of the bibliographical data identified (scientific argument), is available on the HAS website (https://www.has-sante.fr/jcms/p_3346137/fr/syndrome-gilles-de-la-tourette). In brief, the PNDS are elaborated by a panel of French experts on TS based on a systematic review of the literature. The panel also includes representatives from patient organizations. A formal consensus was obtained. Finally, these guidelines are updated every five years on average. The present version (2022 in French) is the second one, the first having been elaborated in 2016.

3. Initial diagnosis and evaluation

3.1. *Objectives*

The clinician must start by confirming the presence of tics. Tics can be distinguished from other abnormal movements by a number of semiological features. Tics are unique in that they can be, at least temporarily, suppressed by patients, but this often requires a considerable amount of effort.

Tics are often accompanied by unpleasant premonitory sensations or thoughts. Premonitory phenomena can manifest themselves, for example, as a burning sensation or tension that the tic will more or less relieve. These premonitory phenomena result in an urgent need or desire to perform the tic. This phenomenon is called ''urge to do'' or ''urge to move''. It should be noted that these urges mainly appear from adolescence onwards and are therefore often not clearly identifiable in children under the age of 10.

The differential diagnosis of tics includes all types of repetitive abnormal movements and semiology alone is never sufficient to diagnose a tic with certainty. The clinician must therefore ensure that the following conditions exist:

- a premonitory urge;
- a control, however brief, of the movement or phonicization and;
- a feeling of relief once they have been carried out.

These three criteria do not necessarily all have to be met, but their complete absence suggests an etiology other than a tic. However, to date, there are no additional tests or biomarkers (MRI, EEG, electromyoneurography, blood tests) that can positively validate the diagnosis of tics; at best they can help to rule out differential diagnoses (e.g. epilepsy) [6].

Next, there must be the presence of at least two motor tics and one phonic tic over a period of at least one year to meet DSM-5 criteria, and the tics must have started before the age of 18 (see Online supplement Annex 1). Secondary causes should also be excluded (cocaine, amphetamines, lamotrigine, Huntington disease, neurodegeneration with brain iron accumulation, Lyme disease, Wilson disease, fragile X syndrome, viral encephalitis), although these types of investigation are very seldom necessary in practice.

3.2. *Health professionals involved (and coordination modalities)*

GP or school doctors/nurses (or occupational physicians in adults in the event of a late diagnosis) are often the first to see patients with TS. If tics are suspected and social or functional discomfort is present, the opinion of a specialist should be sought, according to the patient's age (psychiatrist/child psychiatrist; neurologist/pediatric neurologist). The specialist will determine tic severity and impact, and the presence or absence of comorbidities. The GP will participate in the

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management and prescribe treatments. The GP will also play an important role in prescribing rehabilitation therapies if necessary and in ensuring accommodations at school and at work.

3.3. *Circumstances of discovery/suspicion of diagnosis*

The family is often the first to suspect TS due to a lack of knowledge of the condition in medical, psychological and educational circles (the average delay between symptom onset and diagnosis is estimated at 5 years, which equates to a major diagnostic wandering for the patient). As a result, it is not uncommon for patients or their families to seek a specialist consultation themselves, often following a search on the Internet.

Phonic tics in particular cause problems: when they are simple (sniffing, coughing, throat clearing), they are often not recognized as such. On the other hand, the presence of complex phonic tics such as palilalia (repetition of one's own words), echolalia (repetition of others' words) and, in particular, coprolalia (obscene language) are neither frequent nor mandatory for making the diagnosis of TS but continue to be considered as such by many. In practice, patients with simple motor tics such as eye blinking are often seen by ophthalmologists on suspicion of conjunctivitis, or by pulmonologists on suspicion of asthma in the case of a cough [7].

There can also be confusion between tics and OCD in French. While OCD (TOC in French) is an abbreviation for ''obsessive-compulsive disorder'', tic is an onomatopoeia or derivative of *ticchio*, which means ''caprice'' in Italian. Nevertheless, there are similarities between complex tics and OCD since both are characterized by repeated, compulsive motor behaviors: touching objects or people, counting, checking, washing, etc. Based on the observation of this type of behavior alone, it is very difficult, if not impossible, to know whether it is a tic or an OCD compulsion: what matters is the experience of the person concerned. For example, a tic is preceded by a premonitory urge and can be partially controlled, but the gesture – and thus the repeated behaviour – is not accompanied by any particular thought and has no specific purpose. Compulsions in the context of OCD, on the other hand, are not preceded by a premonitory urge and cannot be controlled. They are usually preceded by obsessions and are intended to neutralize or diminish anxiety or feelings of distress, or to prevent a feared harmful event or situation.

3.4. *Confirmation of the diagnosis/differential diagnosis*

The major differential diagnoses for tics according to the DSM-5 are: 1) provisional tic disorder (lasting < 1 year); or 2) chronic motor or phonic tics (lasting > 1 year but purely motor or phonic).

The differential diagnoses for repetitive movements are myoclonus, dystonia, chorea, paroxysmal dyskinesia, ballism, hemifacial spasms, stereotypies, compulsions, akathisia, restless legs syndrome and epilepsy [6]. The possibility of a functional neurological disorder should also be taken into account, with sometimes mixed presentations (simultaneous presence of tics and tic-like behaviors) [8]. Additional exams (EEG, MRI, blood tests, electrophysiology) are rarely necessary, unless a diagnosis mentioned above is suspected and can be confirmed by these procedures.

3.5. *Assessment of disease severity/progression, search for comorbidities and assessment of prognosis*

Once tics have been defined as such and differential diagnoses have been ruled out, several points need to be clarified:

- number, severity, frequency (circadian profile) and intensity of tics;
- exacerbating or relieving factors;
- psychosocial consequences (repercussions at school: being teased, repeating grades; repercussions at work: difficulty finding a job, being laid off, missed promotions), physical sequelae (pain, injury), and fatigue due to suppressing tics;
- family functioning;
- comorbidities (OCD, ADHD, behavioral disorders, learning disorders, autism spectrum disorders, mood disorders, anxiety disorders, explosive outbursts);
- pregnancy, delivery, psychomotor development (walking, first words);
- family history – especially of tics, OCD, and ADHD.

Observation of the patient during the consultation is often not very helpful, as patients tend to repress their tics in front of strangers, or reduce their occurrence substantially. It is therefore necessary to rely on the descriptions given by patients and their families, possibly supported by videos shot at home or in another familiar environment.

The use of tic rating scales is possible, the most notable being the Yale Global Tic Severity Scale (YGTSS) [9], which has become the reference tool used in clinical studies involving tics. This is a clinician-rated scale. It should be noted that a validated French version does not exist, and it is therefore administered by clinicians who understand English. In routine clinical use, it does not necessarily provide any added value, but it is indispensable for most clinical studies. A validated version of a TS-specific quality of life scale (GTS-QoL-F), which is patient-rated, has recently become available [10].

The neuropsychological assessment of a patient with ''pure'' TS will not show any abnormalities. On the other hand, it is clearly indicated in cases of suspected ADHD, learning disorders or intellectual disability.

A more thorough psychiatric evaluation, possibly using appropriate scales, will depend on the presence and impact of comorbidities. Several types of psychiatric disorders have been described in TS patients. Whether these psychiatric manifestations are an integral part of the syndrome or merely an association is a matter of controversy. Nevertheless, it is important to note that these disorders affect approximately 85% of patients [1], making TS a quintessential neuropsychiatric disorder that requires multidisciplinary management and care. More generally, tics and their ''classic'' comorbidities are neurodevelopmental disorders associated with delayed brain maturation. In this context, we need to think in terms of circuitry rather than focal lesions.

Individual prognosis is, to date, impossible to determine. In particular, the possibility of improvement/remission in adulthood, generally described in cohorts of patients, and which

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may reassure patients and their parents, is difficult to generalize at the individual level [2].

3.6. Searching for treatment contraindications

Since pharmacological treatments are generally based on the use of antipsychotics, it is the specific contraindications to this type of medication that should be sought or excluded, i.e.,:

- clinically significant cardiac manifestations (recent myocardial infarction, decompensated heart failure);
- QTc interval prolongation;
- history of ventricular arrhythmia or ''torsades de pointes'';
- uncorrected hypokalemia.

It is strongly recommended to perform an ECG when starting treatment.

An annual metabolic workup is also recommended and may include analysis of the following elements:

- complete blood count (CBC);
- platelet count;
- aminotransferases;
- creatine phosphokinase (CPK);
- thyroid-stimulating hormone (TSH);
- total cholesterol, HDL, VLDL;
- triglycerides;
- prolactin;
- fasting blood glucose;
- hemoglobin A1C (HbA1C);
- 25-OH vitamin D3.

3.7. Communicating the diagnosis and informing the patient

We have developed a framework for communicating the diagnosis, as follows.

3.7.1. Introduction

The diagnosis of TS is generally made after a period of major diagnostic wandering, with a significant number of self-diagnoses (via the internet, television). The diagnosis is often traumatic for the parents concerned. This is largely due to the negative media coverage of TS, which is depicted as a psychiatric condition that almost inevitably leads to social isolation and dropping out of school. The main idea in the ''collective imagination'' is that coprolalia must be present as a symptom. Other fears are fueled by the presence of psychiatric comorbidities, which are perceived as equally inescapable, such as ADHD, OCD or learning disorders. Finally, the prognosis is generally unclear. It is therefore imperative to explain this condition in clear terms. The following points should serve as a guide for conducting the diagnostic interview calmly and without haste.

3.7.1.1. Explanations and reassurance. Here are some explanations and reassurances that can be offered to patients and families:

- explain the DSM-5 criteria used for diagnosing TS;
- explain that TS is a more common disease than generally acknowledged;
- explain the continuum in the severity of symptoms (mild to severe forms);
- explain the fluctuations observed in the expression of tics (type, frequency, intensity) over time;
- explain the major comorbidities (ADHD, OCD, impulsivity, etc.);
- emphasize the fact that TS significantly improves in two-thirds of cases in adulthood. This point is particularly important for parents, who are often very worried;
- mention famous people with tics (e.g. André Malraux, Billie Eilish, Lewis Capaldi);
- explain that if tics persist into adulthood, they are often more easily managed/accepted than in childhood/adolescence.

3.7.1.2. Education and professional activity. Below, some relevant information on education and professional activity in individuals with TS:

- in theory, normal academic and professional activity is the rule, not the exception;
- it is important to communicate about the disease at school, in the workplace or in sports settings;
- there is the possibility of special accommodations (for people with a disability)

3.7.1.3. Treatments. Establish the psychosocial and/or functional disability caused by tics:

- healthy lifestyle habits (sleep/wake, sports);
- cognitive-behavioral therapies (CBT);
- medications;
- botulinum toxin;
- surgery.

3.7.1.4. Documentation. Documentaion on TS and comorbidities can be found here:

- guides (such as the French language guide on tics https://www.chu-montpellier.fr/fileadmin/medias/Publications/La-petite-notice-des-tics-pour-enfants-et-adolescents.pdf) and dedicated websites at the national (French Patient Association for Tourette syndrome, French National Reference Centre and Network) or international (European Society for the Study of Tourette Syndrome; ESSTS) level.

3.8. Genetic counseling

The genetic component of TS is undeniable: 50% of monozygotic twins compared to around 8% of first-degree relatives show a concordance for TS, and these figures increase to 77% and 23%, respectively, when only simple tics are considered.

The genetics of TS, however, is probably very complex [11]. Several models of inheritance have been proposed, based on studies of families with tics of varying severity. Recent studies

favor the hypothesis of polygenic inheritance, with an additive effect of the genes involved.

To date, no major gene involved in the inheritance of TS has been identified, therefore neither molecular diagnosis nor presymptomatic diagnosis is possible in practice. Genetic counseling can be summarized as a clear and appropriate statement of the often familial nature of tics (and/or comorbidities), explaining the increased relative risk (the absolute risk remaining low) for relatives of an affected patient, without going into details and making sure to provide reassurance. Given that TS is a treatable disorder with an overall good prognosis, it is not advisable to discourage or worry potential future parents, especially if they are affected by TS themselves. It is also important to stress that ''genetic'' does not necessarily mean ''systematically passed on to offspring''. Recent findings suggest that the role of new or *de novo* mutations is just as important as mutations inherited from parents.

4. Therapeutic management

4.1. *Objectives*

The treatment of tics must be both pragmatic and based on controlled studies, which, unfortunately, remain rather scarce. The first essential step is to advise and inform the patient, their family and their school or work environment about the nature of the tics, the comorbidities and the prognosis (psychoeducation). In most cases, these simple measures, accompanied by regular follow-up, will suffice. It should be noted that therapeutic patient education (TPE) programs for patients and their families are either already in place or under development for TS in France. TPE will undoubtedly be an important tool in the management of tics and any comorbidities.

The decision to treat a tic is based on four criteria:

- the tics cause social problems (social isolation, teasing, bullying);
- the tics have significant emotional consequences (low self-esteem, reactive depression, social anxiety disorder);
- the tics have functional consequences in everyday life (reading, writing, concentration, fatigue). The tics cause pain, injury and/or physical disability.

As with all movement disorders, the objective severity of tics is not linearly related to the subjective impairment. Furthermore, it is important to emphasize that the goal should not be to completely eliminate tics, in order to have a reasonable objective for follow-up and to avoid therapeutic escalation, which can be harmful.

It is also essential to take into account comorbidities (ADHD, OCD, explosive outbursts, depression, anxiety, learning disorders, etc.) and prioritize patients' needs. Several studies show that the quality of life of individuals with TS is often more negatively affected by comorbidities than by the tics themselves. It is therefore always worthwhile, whenever possible, to propose multidisciplinary management. Although the treatment of comorbidities is beyond the scope of these recommendations, two key points are worth mentioning:

- firstly, antidepressants have limited efficacy in children; in the case of depression in minors, psychotherapy is essential. On the other hand, selective serotonin reuptake inhibitors (SSRIs) can be useful in treating anxiety and OCD [12];
- secondly, in cases of ADHD, psychostimulants (methylphenidate) are not contraindicated in TS, even if there is a slight risk of exacerbating tics. Introducing an antipsychotic agent first may help prevent tics from worsening when methylphenidate is introduced later. If tics worsen with methylphenidate, a slight increase in the dose of the antipsychotic may also be considered [13].

Finally, treating comorbidities can have an indirect beneficial effect on tics by reducing tic-related stress, anxiety and depression.

In addition to the medical disciplines involved in the care of TS (psychiatry/child psychiatry, neurology/pediatric neurology), the management of learning disorders (with neuropsychological assessments, speech therapy, psychomotor therapy and occupational therapy) and social support (extra time during exams, private assessments, teaching assistants) can be of great benefit.

4.2. *Professionals involved (and coordination modalities)*

The specialists involved in the management of TS are child psychiatrists/psychiatrists and pediatric neurologists/neurologists. They are responsible for coordinating care, which also involves other healthcare professionals:

- clinical psychologists (CBT, supportive psychotherapy);
- neuropsychologists (cognitive assessments);
- speech therapist (reading and writing difficulties);
- psychomotor therapists and occupational therapists (motor disorders);
- physiotherapists (musculoskeletal pain);
- social workers (accommodations at school and at work).

In addition, ongoing liaison with referring physicians (general practitioners, school nurses or occupational health physicians) is essential.

4.3. *Therapeutic management*

4.3.1. *Introduction*

Several medicinal products mentioned in this PNDS are used for the therapeutic management of children (for an indication or under conditions of use not specified in the French Marketing Authorization).

Only haloperidol, pimozide and tiapride have marketing authorization in France for the treatment of tics, and of these, only haloperidol has data on its use in pregnant women, available in the summary of product characteristics. The French recommendations are largely based on European recommendations [4]. For an overview of the practices in

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North America, the guidelines of the American Academy of Neurology (AAN) can be consulted [14]. There are many similarities between the two, apart from the emphasis on the primary pharmacological treatment: in North America, alpha-2 agonists are favored, whereas in Europe, antipsychotics tend to be prescribed as first-line treatment [15].

4.3.2. *Pharmacological approaches*

When pharmacological treatment is considered, a number of points need to be clarified with patients and parents, where appropriate:

- treatments are symptomatic, not curative;
- they consist of long-term treatment, to be taken regularly over periods of at least several months, often years;
- the goals set must be realistic, with a desired reduction in tics of 30–50% as a rule of thumb. Otherwise, self-medication and overmedication may be observed;
- nevertheless, especially in children and adolescents, a reduction or even interruption of treatment once a year (usually during summer vacation) may be considered in order to assess the basal state of the syndrome and subsequently decide whether or not to continue treatment, particularly during the period when spontaneous remission of tics (around the ages of 16–20) becomes likely.
- The fluctuating evolution of tics, especially in children and adolescents, must be emphasized. In concrete terms, a treatment may be judged as ''ineffective'' or even detrimental if it is initiated during a period of increasing tics; conversely, a treatment may be prematurely judged as ''effective'' because it is initiated during a period of spontaneous remission. In our opinion, a treatment observation period of at least 3 months is the best way to avoid these biases, provided, of course, that the treatment is well tolerated.

Historically, the treatment of tics has been essentially based on the use of antipsychotics (dopamine receptor antagonists), primarily with haloperidol. Among the so-called ''typical'' antipsychotics (due to their particular affinity for D2 dopamine receptors), pimozide appears to be as effective as haloperidol, with fewer side effects, particularly in terms of lethargy and weight gain, as well as the occurrence of extrapyramidal symptoms. However, QT intervals need to be monitored closely. Over the past two decades, specialists have favored the so-called ''atypical'' antipsychotics, because of their lower affinity for D2 receptors, which reduces the risk of parkinsonism and tardive dyskinesia. Among these, risperidone offered the best level of evidence until a few years ago; nevertheless, the metabolic side effects of this treatment (weight gain, hyperglycemia, increased triglyceride and prolactin levels) are significant and need to be closely monitored. There is also a risk of depression due to the antiserotonergic effects of this drug.

Aripiprazole has a specific mechanism of action, being a partial agonist of D2 and 5-HT1A receptors and an antagonist of 5-HT2A receptors. Recent randomized studies in children and adults show a significant efficacy of this drug on tics, with milder sedative and orexigenic effects than those of other antipsychotics. A positive behavioral effect (calming and anxiety-reducing) is also frequently reported by patients and/or their parents. A beneficial effect on falling asleep has also been noted.

Finally, among the ''atypical'' antipsychotics, tetrabenazine, a monoamine-depleting drug, offers the potential advantage of not inducing tardive dyskinesia. However, its use is limited by its significant sedative effect and associated high risk of depression, and we consider it to be a third-line treatment. Of note, there is no RCT-based evidence that tetrabenazine is superior to placebo in treating tics, even though it has long been used on an empirical basis.

With regard to extrapyramidal syndromes and tardive dyskinesias following the use of antipsychotics, a few clarifications are necessary. Firstly, the doses used to treat tics are in the vast majority of cases much lower than those used to treat psychosis, which potentially limits the occurrence of these types of undesirable effects. Even more interesting is the near-total absence of extrapyramidal syndromes and tardive dyskinesias in minors, raising the question of whether TS ''protects'' against these types of adverse effects. For the time being, robust studies to conclusively answer this question are lacking. Pragmatically speaking, however, we believe that a reluctance to prescribe antipsychotics to minors is unjustified, and should not exclude the use of these drugs in reasonable doses, if the indication is clearly defined.

Another group of drugs that have been in use for several decades are alpha-2 adrenergic receptor agonists, which include clonidine. This drug has been evaluated in controlled clinical trials and found to be effective in the treatment of tics. Its efficacy is generally inferior to that of antipsychotics. Consequently, clonidine's interest lies more in the treatment of behavioral disorders (particularly hyperactivity) and ADHD, rather than tics per se. However, if the tics are not too severe and comorbid ADHD is present, this drug may offer an interesting profile.

Among the antiepileptic drugs, topiramate has been proposed as beneficial in the treatment of tics in a randomized trial, which also reflects our clinical impression after a decade of regular use. One of topiramate's remarkable side effects is a reduced appetite. Thus, in combination with an antipsychotic or as monotherapy after treatment with antipsychotics, a reduction in weight can often be achieved. Topiramate also has anti-impulsive properties. Of note, topiramate is potentially teratogenic and its use must be closely monitored in women, with adequate contraception being mandatory.

Overall, aripiprazole is our first drug of choice for the treatment of tics, and this is also reflected in the North American and European guidelines. Despite the availability of high-quality studies, aripiprazole has no marketing authorization for this indication in France. It should be noted that aripiprazole is available as a drinkable (liquid) solution and can therefore be given in very low doses (starting at 1 mg a day, or even 0.5 mg in some cases) that can be easily and precisely adjusted and are often sufficient and effective, within a usual therapeutic range of 2 and 5 mg (in both children and adults), and only rarely requiring doses up to 10 mg or higher.

In addition, we emphasize the potential utility of botulinum toxin for isolated tics. Botulinum toxin offers the

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advantage of a targeted and transient, but repeatable, procedure for the treatment of certain severe and potentially dangerous tics (notably whiplash tics involving the neck). Similarly, an injection into the phonic cords is sometimes effective in treating severe phonic tics.

As for the use of medical cannabis or active compounds derived from cannabis (THC, CBD) in the treatment of tics, several studies have been published recently but with mixed results. It is therefore not possible to issue recommendations on this subject, despite widespread public interest in these approaches. Also, THC-based products are not licensed for the treatment of tics at present in France.

Online supplement Annex 3 summarizes the major pharmacological treatments currently available in France for the treatment of tics. Therapeutic recommendations have been formulated at the European level by the European Society for the Study of Tourette Syndrome (ESSTS) in 2022 [16] and the American Academy of Neurology (AAN) in 2019 [14].

4.3.3. *Psychotherapeutic interventions*

Psychotherapeutic approaches, particularly cognitive-behavioral therapies (CBT), are now considered first-line treatments in both the North American (AAN) and European (ESSTS) guidelines [14,17]. Furthermore, they are potentially useful for all tics regardless of their severity; thus, in the presurgical screening of patients considered severe and treatment-resistant, these should no longer include only pharmacological treatments, and an attempt at CBT intervention is also recommended.

Among the many techniques studied to date, it is primarily habit reversal training (HRT) that has obtained a high level of evidence (more so than pharmacological treatments). The most widely used, updated version of this approach is called comprehensive behavioral intervention for tics (CBIT). Essentially, the patient learns antagonistic movements or movements that compete with the motor or phonic realization of the tics, thereby inhibiting them. The technique also includes relaxation training, as well as self-monitoring and self-reward techniques when a tic is not carried out. Another technique, also part of the cognitive-behavioral register, is exposure and response prevention (ERP), which involves gradual habituation to tic suppression while avoiding the rebound phenomenon. Other techniques, such as attentional strategies, are currently being developed but need to be validated.

A key factor to consider is the patient's motivation to pursue this type of therapy, as it involves daily work (in the therapist's presence and in between the weekly sessions) for approximately 3–6 months. A certain degree of introspection is also required, particularly concerning the presence of premonitory urges, to ensure that CBT runs smoothly. These two points do not exclude, but rather limit the use of these therapies in minors, particularly in children under ten, for whom antipsychotics, albeit at very low doses, are therefore usually the first-line treatment.

A list of therapists trained in cognitive-behavioral therapy (CBT) for tics in France can be obtained from the Reference Center for Tourette syndrome (*Centre de référence national syndrome Gilles de la Tourette*; CRMR SGT). Remote treatment and follow-up (via video-consultations) appear to be effective and became widespread during the COVID-19 pandemic, facilitating access to trained therapists. In addition, several computer programs are currently being validated (BT-Tics, ONLINE Tics, TicHelper, BipTic) which will further promote the accessibility of these approaches to a broader audience.

4.3.4. *Neurosurgical interventions*

Deep brain stimulation (DBS) offers considerable therapeutic promise in the treatment of drug- and CBT-resistant tics. To date, it is estimated that around 500 individuals with TS have undergone this procedure worldwide. The major targets tested are the globus pallidus internus (GPi) (sensori-motor and limbic territory) and the thalamus (medial and intralaminar nuclei). The surgical indication is determined by a multidisciplinary team following international and national consensus criteria, but is constantly evolving [18].

4.3.4.1. *Conclusions*. In practice, we propose an approach adapted from the ESSTS recommendations, as well as a treatment decision tree (Online supplement Annex 1 Fig. S2) [6,16]:

- mild tics (which do not interfere with schooling, socialization or family life) do not generally require treatment;
- for moderate tics (meaning they cause difficulties in schooling, socialization, or family life), treatment with CBT, if available and feasible, should be considered. From a pharmacological standpoint, low-dose aripiprazole (between 1 and 5 mg per day) is the first choice of treatment;
- for severe isolated tics, attempt treatment with botulinum toxin injections;
- severe tics should also be treated with aripiprazole (at higher doses than for moderate tics: up to 10–15 mg/day). If this treatment proves to be insufficiently effective, the addition of topiramate (up to 100 mg/day) is recommended. Subsequently, other drugs such as pimozide, haloperidol, tiapride, risperidone, clonidine and tetrabenazine can be tried;
- finally, when pharmacological and cognitive-behavioral treatments fail, DBS is a last resort for severe forms.

4.4. *Therapeutic patient education and lifestyle modification (on a case-by-case basis)*

Specific therapeutic patient education programs for the treatment of TS are currently being developed and implemented throughout France. At times, however, it may be necessary to modify the patient's lifestyle: partial withdrawal from school, boarding school, reduced working hours and/or workplace accommodations. These decisions are taken jointly with the social services. Therapeutic patient education often involves parents. Contact with the school environment (school doctors/nurses, teachers, psychologists) is also often necessary.

4.5. *Seeking support from patient organizations*

Since it was founded in 1997, the French Patient Association for Tourette Syndrome (AFSGT – *Association française du syndrome de Gilles de la Tourette*) has played a major role in

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educating people about TS, guiding patients towards appropriate care, and supporting families through difficult times by providing a hotline and appropriate assistance (https://www.france-tourette.org). One of the AFSGT's most useful contributions, according to patients and their families, is its regional and national meetings (general assembly, summer camps, information meetings). These give patients and their families the opportunity to talk about their difficulties and the strategies and tools they have adopted. Patients are also offered emergency cards, which are designed to help better understand these types of situations. Similar resources are available from patient organizations in many other countries.

5. Follow-up

5.1. *Objectives*

The aim of management and care is to ensure that patients remain integrated into school, work and family life, and to improve their well-being in the face of a condition that carries a strong social stigma, and in some cases has functional consequences.

As TS is characterized by the presence of motor and phonic tics, the first objective is to monitor them and, if necessary, reduce them by the appropriate means.

Next, comorbidities need to be assessed on an equally regular basis, and appropriate management proposed. This should be done in conjunction with all healthcare professionals involved, and, if necessary, they should be reduced by appropriate means (see section 5.2).

5.2. *Professionals involved (and treatment modalities)*

The healthcare professionals involved in the follow-up of patients with TS are:

- clinical psychologists (CBT, supportive psychotherapies);
- neuropsychologists (cognitive rehabilitation);
- speech therapists (troubles with reading and writing);
- psychomotor therapists and occupational therapists (motor disorders);
- physiotherapists (musculoskeletal pain);
- social workers (school and work accommodations).

During follow-up, ongoing communication (letters, assessments, telephone calls, multidisciplinary meetings) between these professionals is necessary and must be coordinated by the medical specialists directly involved with TS, in other words, pediatricians, child psychiatrists/psychiatrists and pediatric neurologists/neurologists.

5.3. *Frequency and content of consultations*

Consultations can be at a frequency of once or twice a year for cases without major complications. The severity of tics rarely warrants hospitalization. Psychiatric comorbidities are treated on an outpatient basis in the majority of cases; indications for hospitalization linked to psychiatric disorders include behavioral disorders (impulsivity, aggression), mood disorders (depression) and risk of suicide. Also, if available, we insist on the value of multidisciplinary consultations. These consultations bring together psychiatrists, neurologists, clinical psychologists and social workers, in order to carry out an in-depth assessment of TS patients and identify the current management and care needs for them and their families. Each appointment must lead to concrete proposals regarding the management and follow-up of patients, both in terms of pharmacological and therapeutic aspects, as well as social, educational, and/or professional aspects. Annual general check-ups are also recommended, including an ECG and blood tests if antipsychotics are prescribed (see section 3.6).

6. Medical-social support

Social support for patients with TS generally focuses on two areas: schooling and work. Indeed, their educational and/or career paths can be more complicated due to the symptoms of TS (phonic and motor tics) and various comorbidities (attention deficit disorders, learning disorders, etc.).

We regularly meet patients' families who describe how difficult it is for them to attend school, and how difficult it can be for school staff to understand TS and propose appropriate solutions. The first step after diagnosis is therefore to provide the family with as much information as possible on the impact of TS, which can then be passed on to the school by the parents. In France, the *Association française du syndrome Gilles de la Tourette* (AFSGT – https://www.france-tourette.org/article/le-guide-de-leducateur) has produced a document for school staff with this in mind, and similar documents are available in other countries. Tics, particularly phonic tics, are often a source of tension and misunderstanding at school, as they can be perceived as a deliberate attempt to disrupt the class. Explaining these symptoms to the teacher is already a start towards easing relations and initiating a discussion on the appropriate solutions to ensure that the expression of tics is better tolerated. In most cases, it is therefore possible for the child to attend a mainstream school. Comorbidities, such as learning disorders and attention deficit disorders, also need to be monitored and taken into account in the social support of students, as they can often be more detrimental to their education than the tics themselves. Some students will need a slightly more adapted form of schooling and will have to turn to specialized classes or schools.

In adults, access to employment and sometimes job retention can be complicated by tics and comorbidities and here too they are often misunderstood by employers. Some tics may be incompatible with certain tasks (for example, if they endanger the patient or others). It is therefore essential to refer patients to employment support agencies that can propose jobs or trainings that take certain restrictions into account. In most situations, employment in an ordinary environment is possible and recommended. However, for certain individuals, a more specialized form of support is required such as what is offered at an *Établissement ou service d'aide par le travail (ESAT)*, to take the example from France. It is a service providing support and employment opportunities for individuals with disabilities.

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Ultimately, medical-social support plays a significant role in the care of these pediatric or adult patients and should aim to find solutions to address all these challenges as effectively as possible, ensuring that their education and professional life proceed as smoothly as possible. Several forms of assistance exist and can be requested.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors thank the BRAIN-TEAM network (www.brain-team.fr) for its support in the preparation of the manuscript, and Mrs. Natasha Barr for translation.

Online supplement. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2024.04.005.

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