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Gilles de la Tourette Syndrome: an update on the treatment of paediatric patients

Núria Condé Pinto Gusmão Fonseca

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Mestrado Integrado em Medicina

GILLES DE LA TOURETTE SYNDROME: AN UPDATE ON THE TREATMENT OF PAEDIATRIC PATIENTS

Artigo de Revisão Bibliográfica

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Resumo

Introdução: A Síndrome de Gilles de la Tourette é uma doença neuropsiquiátrica com início na infância, caracterizada por tiques motores e fónicos presentes durante pelo menos um ano, frequentemente associados a outros sintomas. Apesar da crescente investigação, muitas questões sobre a sua etiologia e abordagem terapêutica não são ainda consensuais. As últimas *guidelines* europeias dedicadas a esta patologia *(European Clinical Guidelines for Tourette Syndrome and other tic disorders)* datam de 2011. Desde então, novas evidências têm surgido.

Objetivos: Sistematizar conceitos importantes para o diagnóstico e avaliação dos doentes com Síndrome de Gilles de la Tourette. Rever a literatura sobre o seu tratamento na população pediátrica, sugerindo um protocolo de tratamento para o serviço de Neuropediatria do CMIN-CHUP.

Metodologia: A pesquisa foi realizada utilizando o motor de busca PubMed e selecionando apenas artigos em inglês. Esta foi inicialmente focada na apresentação, epidemiologia, etiologia e fisiopatologia. Apenas as publicações mais relevantes foram incluídas, num total de 76 artigos e capítulos de livros. Numa segunda fase, a pesquisa foi direcionada ao tratamento, selecionando os artigos publicados entre 1 de abril de 2011 e 30 de setembro de 2018 (período entre a publicação das *guidelines* e o início do trabalho). Destes foram selecionados 72 artigos, sobretudo meta-análises e estudos com amostras superiores a 50 participantes. Artigos de revisão e pequenas séries foram incluídos quando pertinentes.

Desenvolvimento: A Síndrome de Gilles de la Tourette caracteriza-se por tiques e outros sintomas cuja elevada prevalência permite considerar como comorbilidades. Fatores genéticos, ambientais e imunológicos têm sido avançados como determinantes na sua etiologia, e modelos neurológicos têm sido estabelecidos, permitindo um melhor entendimento da sua fisiopatologia. Para a avaliação dos doentes, existem já escalas clínicas. A intervenção psicossocial deve ser sempre assegurada, e individualmente formulada uma abordagem terapêutica (terapia comportamental e/ou farmacoterapia). O tratamento das comorbilidades assume grande importância, a par com o tratamento dos tiques. Muitos fármacos mostram-se promissores, ainda que alguns usados *off-label.* A estimulação cerebral foi já documentada na população pediátrica, em casos refratários.

Conclusões: A terapia comportamental é fortemente sugerida como primeira linha, com benefícios reportados na literatura internacional, associada a farmacoterapia, se necessário. A risperidona é o fármaco mais prescrito para os tiques na Europa, mas o aripiprazole e as benzamidas têm já sido muito usados, devido aos seus bons resultados. Em Portugal, é necessária uma mudança de paradigma, com a introdução da terapia comportamental e uma avaliação multidisciplinar dos pacientes. A investigação neste tema mostra-se de suma importância, pois não obstante o

crescente conhecimento da patologia, em todas as suas dimensões a maior limitação é ainda a falta de resultados baseados na evidência.

Palavras-chave: Síndrome Gilles de la Tourette, Tiques, Perturbações de tique, Criança, Adolescente, Pediatria, Terapia Comportamental, Terapia Farmacológica, Estimulação Cerebral Profunda

Abstract

Introduction: Gilles de la Tourette Syndrome is a neuropsychiatric disease that begins in childhood, characterized by motor and phonic tics, present for at least one year, often associated with other symptoms. Despite the growing research, many issues associated with its aetiology and therapeutic approach are not yet consensual. The last European guidelines for this pathology (European Clinical Guidelines for Tourette Syndrome and other tic disorders) were published in 2011. Since then, new evidence has emerged.

Objectives: To systematize important concepts for the diagnosis and evaluation of patients with Gilles de la Tourette Syndrome. To review the literature on its treatment in the paediatric population, suggesting a treatment protocol for the CMIN-CHUP Neuropediatrics service.

Methodology: The research was conducted through PubMed, selecting only articles in English. This was initially focused on presentation, epidemiology, aetiology and pathophysiology. Only the most relevant publications were included, in a total of 76 articles and book chapters. In a second phase, the research was directed to the treatment, selecting articles published between April 1, 2011 and September 30, 2018 (the period between the guidelines' publication and the beginning of this review). Of these, 72 articles were selected, mainly meta-analysis and studies with more than 50 participants. Review articles and small series were included, when relevant.

Development: Gilles de la Tourette syndrome is characterized by tics and other symptoms whose high prevalence allows to consider as comorbidities. Genetic, environmental and immunological factors have been advanced as determinants in their aetiology, and neurological models have been established, allowing a better understanding of their pathophysiology. For patient evaluation, there are already clinical scales. Psychosocial intervention should always be ensured, followed, if necessary, by an individualized therapeutic approach (behavioural therapy and / or pharmacotherapy). The treatment of comorbidities is of great importance, along with the treatment of tics. Many drugs appear to be promising, although some are still being used off-label. Brain stimulation has been documented in the paediatric population in refractory cases.

Conclusions: Behavioural therapy is strongly suggested at first-line, with benefits reported in the international literature. If needed, pharmacotherapy should be given. Risperidone remains the most prescribed drug for tics in Europe but aripiprazole and benzamides are already been chosen, due to their proved good results. In Portugal, a paradigm change is needed, with the introduction of behavioural therapy and a multidisciplinary evaluation of each patient. In all therapeutic modalities, the lack of evidence-based results seems to be the major limitation, underlining the importance of further research.

Key-words: Tourette Syndrome, Tics, Tic Disorders, Child, Adolescent, Pediatrics, Behavior Therapy, Drug therapy, Deep Brain Stimulation

List of abbreviations

aDBS - adaptative DBS
ADHD - Attention Deficit Hyperactivity Disorder
ALIC - internal capsule's anterior limb
AM - Autonomic Modulation
BF – Bioneurofeedback
BG - Basal Ganglia
BS - Brain Stimulation
BT - Behavioural Therapy
CANS - Childhood Acute Neuropsychiatric Syndrome
CBD - cannabidiol
CBGTC - cortico-basal ganglia-thalamus-cortical
CBIT - Comprehensive Behaviour Intervention for Tics
CBT - Cognitive Behavioural Treatment
cm - centro-median
CM - Contingency Management
CMIN-CHUP – Centro Materno-Infantil do Norte- Centro Hospitalar Universitário do Porto
CNS - central nervous system
CNV - Copy Number Variation
CPT - Cognitive Psychophysiological Treatment
DAT - dopamine active transporter
DBD - Defiant Behaviour Disorders
DBS - Deep Brain Stimulation
DSM-V - Diagnostic and Statistical Manual of Mental Disorders
EEG - electroencephalography
EPS - extrapyramidal symptoms
ERT – Exposure and Response Prevention
FBI - Functional Based Interventions
FDA - Food and Drug Administration
fMRI - functional magnetic resonance imaging
GAS – group A streptococcus
GPi - internal globus pallidus
HRT - Habit Reversal Therapy
ICD-10 - International Statistical Classification of Diseases and Related Health Problems
MBSR - Mindfulness-based Stress Reduction
MNP - Massed Negative Practice
NA - nucleus accumbens
NF - Neurofeedback
OCD - Obsessive-Compulsive Disorder
OCS - Obsessive-Compulsive Symptoms
PANDAS - Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PANS - Paediatric Acute-Onset Neuropsychiatric Syndrome
PET - positron emission tomography
Pf – parafascicular
PI - Psychosocial Intervention
PITANDS - Paediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders
PT - Pharmacological Therapy
PU – Premonitory Urges
RT - Relaxation Treatment
SM - Self-monitoring

SMA - supplementary motor area
SNc - subtantia nigra pars compacta
SSRI - selective serotonin reuptake inhibitors
STN - subthalamic nucleus
TCM - Traditional Chinese Medicine
tDCS - Transcranial direct current stimulation
TEC - theory of event coding
TMS - Transcranial Magnetic Stimulation
TS - Tourette Syndrome
USA – United States of America
VMAT2 - vesicular monoamine transporter 2
VNS - Vagus Nerve Stimulation
Voi - ventralis-oralis
YGTSS - Yale Global Tic Severity Scale
δ-9-THC – tetrahydrocannabinol

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Introduction

Tourette Syndrome (TS) is a neuropsychiatric condition whose main clinical features are tics, both motor and phonics. Therefore, it is at first classified as a Tic Disorder. Symptoms usually begin around the age of five years old. There is evidence that earlier presentations are associated with more speech disfluencies and oppositional defiant disorder but not with more severe clinical presentation. Tics' severity is maximal at the beginning of adolescence tending to diminish, and sometimes disappearing by adult age. However, sometimes symptoms persist or even get worse through adulthood, which is suggested to be related to symptoms' severity in late childhood.[1–4]

Although the lack of accurate epidemiological data on TS, recent meta-analises estimate its global prevalence to be inferior to 1% in the paediatric population, with a predominance in males, as in other neurodevelopmental disorders. Difficulties in accessing an accurate prevalence, may be related to the lack of population-based studies, underdiagnosis and difficulty to distinguish TS from other Tic Disorders (Chronic and Transient) due to their presentation as a spectrum and not separated nosological entities.[5,6]

The most recent diagnostic criteria for TS are established in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). All of them must be present to make the diagnosis (table1). According to the European Clinical guidelines for Tourette Syndrome and other tic disorders, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), which overrides de DSM-V criteria, may also be used.[2,7]

Despite the recent investigation, the right assessment of this pathology is not well defined, due to questions on the aetiology and differential diagnosis of tics. Moreover, there are associated symptoms and comorbidities that, although not mandatory for the diagnosis, are often implicated in its presentation, influencing treatment and prognosis.

Objectives

To review some important concepts to distinguish tics from other movement disorders and establish the diagnosis and evaluation of TS patients.

To review the recent worldwide literature on TS treatment in the paediatric population, to suggest a treatment protocol to be used in the Neuropediatrics department of CMIN-CHUP.

Methods

Research in TS was conducted through PubMed, selecting only articles in English.

First, it was focused on its clinical presentation, epidemiology, aetiology and physiopathology. Only the most relevant publications in English were included, in a total of 76 articles and book chapters.

At the second phase, the research was focused on the treatment of TS in the paediatric population, selecting articles published between 1 April 2011 and 30 September 2018 (the period between the publication of the European Guidelines, and the beginning of this review). All the abstracts were read, and 72 articles were selected, including predominantly meta-analysis and studies with more than 50 participants. Review articles and small-series were also included, when relevant.

Development

I. TOURETTE SYNDROME

1. Main concepts

1.1. Tics

First, we must define tics. Tics are brief, sudden, repetitive, non-rhythmic and recurrent movements or phonations. Their presentation is fluctuant ("waxing and waning") in frequency, intensity and hardness. They can be single or multiple and migrate along lifespan. Stress and fatigue seem to increase tics, while the concentration in fine motor actions has the opposite effect.[2,4,8] Typically, simple motor tics appear first, followed by complex and then phonic ones. The distinction between simple and complex motor tics depends on their duration and number of muscles involved. They appear predominantly in the upper part of the body. Simple tics normally involve just a muscle group and are brief. They may be classified as clonic (eye blinking, nose twitching, rapid head movements, tongue protrusion…), dystonic (sustained not-normal positions as blepharospasm, torticollis, rotation on shoulders and bruxism) or tonic (isometric, as abdominal, leg or arm bending).[2,7,9] Complex motor tics generally last longer, involve a greater number of muscles and can mimic normal gestures out of a context, looking more goal-directed. It is the case of head shaking, touching, jumping, hitting, and also echopraxia (imitate other's gestures) and copropraxia (socially inappropriate gestures).[8–11]

Phonic tics may also be simple or complex. Cough, scream, sniffing and throat cleaning are simple phonic tics, while echolalia (repetition of other's speech), palilalia (repetition of part of it, mostly the last syllable) and coprolalia (obscene and insulting context) represent the complex ones.[9–11]

Cognitive tics enclose mental processes such as repetitive fearless thoughts, mental play and echophenomena in thought, which happens due to the need of reacting to internal or external stimuli.[7]

1.2. Premonitory Urges (PU)

Another point is the intention behind tics. They are generally perceived as involuntary but suppressible actions. However, they can diminish, especially during voluntary activities, and some of them are preceded by sensory phenomena which suggest them not to be completely involuntary (semi-voluntary).[9,12] Those phenomena are known as "premonitory urges" or "sensory tics". Although their presence is not a diagnosis criterion, urges are referred by most patients, and some of them consider them more troublesome than the tic itself. They are described as internal unpleasant sensations that suddenly appear, precipitating the need for ticcing, and normally

disappears when the tic is performed. Sometimes it gets worst while the tic is not completed. So, premonitory urges could be considered a "driver"/"impulse" that is perceived as a tension, burn, itch, or even a need for stretch, not associated with the idea that "something bad is going to happen" if they do not tic.[13,14] In some situations, urges are understood as "not-just-right-experiences", which means, a "need to do an action until it is done right", which seems more complex than simple impulses, making it hard to distinguish them from obsessions (intrusive thoughts of harm, anxiety and fear if an action is not performed) and subsequent compulsions (repetitive behaviours performed to avoid a bad closure). However, patients may present both "not-just-right-experiences" and obsessions and many of them have obsessive-compulsive symptoms (OCS) or even obsessive-compulsive disorder (OCD) criteria. So, the limit between tics (especially complex) and compulsions is not obvious. Recently, some authors found that those feelings are more common in patients with TS+OCD/OCS than TS alone. This may have important implications in the elucidation of the common mechanism between these pathologies and even in the treatment of TS patients.[13,15–17]

A practical distinction between tics and other movement disorders is presented in table 2.

1.3. Comorbidities

In TS, tics usually co-occur with other symptoms, presenting a very heterogeneous phenotype. Their recognition is truly important since they are a great cause of impairment, influencing patients' management. The overlap between TS and other pathologies have been studied, and besides all the uncertainties, some evidence has already been shown. 86% of patients are estimated to have criteria for another pathology, and more than a half, for two or more. The most common associated pathologies are OCD and attention deficit hyperactivity disorder (ADHD) and the coexistence of both with TS is frequent. Mood disorders, anxiety and defiant behaviour disorders (DBD), sleep and learning impairment and autism spectrum disorders may also be present. Psychotic disorders are rarer. They are predominantly psychiatric, but correlations between TS and neurologic pathologies as migraine and epilepsy were also postulated. Patients with ADHD and/or OCD, are more susceptible to develop the others. Females are more prone to develop OCD, major depression, anxiety and eating disorders while ADHD, DBD and conduct disorders (such as substance abuse) are more common in males. Age seems to be important, with children manifesting more frequently ADHD, sometimes before tics. However, even before adolescence, there is a high risk of anxiety, OCD and mood disorders.[7,18–20]

TS is also associated with body lesions, especially in adolescence, probably due to tics and consecutive hits and falls (axial fractures), self-defeating actions (scratching, head-banging,…) and impulsive behaviour shown by some patients.[21]

Prevalence studies show that the relationship between some of these pathologies and TS is not just a “by-chance” combination, which makes them “comorbidities”. It seems that they may occur by genetic share with TS or other comorbidities (such as OCD and ADHD) or by epigenetic factors. To understand TS aetiology, it would be important to understand if the co-occurrence of those pathologies is independent (additive), or if in the other hand, they constitute a different pathology with tics and other symptoms (interactive). The hypothesis of a “phenotype model” is then postulated.[18,22] This last arises from the notion that some patients present typical clusters of symptoms and similar (but not necessarily equal) presentations among family members (eg. patients with TS having parents with OCD, with or without tics). So, different pathological neural circuits might lead to different phenotypes. It is consistent with the finding that hereditable risk for OCD with and without tics is different and the sensation that precedes symmetrical behaviours in OCD patients is more related to "urges" than anxiety, as well as tics. Some endophenotypes were proposed, from which we underline the "symmetry" (obsession with symmetry, checking and "writing-rewriting") and "disinhibition" (echo, pali and coprolalia, copropraxia, urge to destroy or mutilate) phenotypes.[22–24] The phenotypic classification might be more accurate than the typical perspective of TS with and without comorbidities.[25,26] In which concerns to ADHD, the correlation mechanism seems different; It is hypothesized that TS and ADHD have an etiologic relationship but, together may constitute an independent entity with specific clinical features, rather than different phenotypes of a common genetic expression, once tics co-occur with ADHD in both patients and their parents.[22–24]

2. Aetiology

2.1. Genetics

Based on clinical evidence, heritability seems preponderant in TS aetiology. So, many types of genetic studies (eg.linkage, candidate gene association, genome-wide association and copy number variation-CNV scan) have been ruled. The transmission mechanism is thought to result from various genetic and epigenetic factors.[27] Despite some genetic variants found, a correlation between them and TS burden is not yet established, once some of them are found in small cohorts or even in single families or patients. Interestingly, their breakthrough is in line with the clinical phenotype and neurophysiological postulates.[28] It is the case of rare CNVs found both in patients with TS and patients with other disorders like OCD and ASD, and a deletion in NRXN1 and duplication in CNTN6, which are synaptogenesis related genes.[29] Histamine's role in dopamine regulation may explain a mutation in the histidine decarboxylase gene, found in some TS patients.[28] Other genes as DRD, SLITRK1 and IMMP2L, which are related to the regulation of different neurotransmitters may be also related to TS, with less consistent evidence.[30]

2.2. Environment

Some environmental risk factors have also been studied. Psychiatric disorders in parents, particularly pre and post-natal anxiety and pre-natal depression in mothers, seem to be related to tic disorders in descendants but it is not clear if this influence is genetic, environmental or both.[31,32] Maternal smoking and pre and perinatal complications were also associated. In the other hand, higher parity and birth weight may be protective factors for TS development[33–35]

2.3. Immunology

The role of immunology in TS pathology is also under investigation. During the last decades of the XX century, several case series started to suggest a link between infections and posterior abrupt onset of neuropsychiatric symptoms which led to the attempt of classifying it in syndromes. The first designation was PITANDS (Paediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders) and then PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) because of the specific correlation between GAS infection and OCS/tics onset. This association was not easy to establish because the temporal relation between the infection and symptoms, as well as the identification of ASO and anti DNAseβ antibodies in patient's serum, were not always possible. Moreover, symptoms other than tics and OCS were reported. So, PANS (Paediatric Acute-Onset Neuropsychiatric Syndrome) and CANS (Childhood Acute Neuropsychiatric Syndrome) were proposed, both with specific criteria. In sum, PANS presupposes

an abrupt dramatic onset of neuropsychiatric symptoms not better explained by other known disorder, while CANS have mono or polyphasic course and may have different aetiologies (eg. infectious, toxic, autoimmune, hypoxic and psychogenic).[36,37]

In TS patients some studies have shown higher titers of antibodies against specific pathogens, as well as autoantibodies and cytokines. The role of microglia is also being studied, with evidence of excessive activation of these cells in TS patients' striatum, and it was also advanced the possibility of a lower number of T regulatory cells (CD4+ CD25+), IgA and IgG_3 among this population. Although these findings might suggest an autoimmune aetiology, this correlation has not found consistent results yet due to the small size of studies samples. It is also questioned if this relation happens because infection triggers immune modulation with direct effects on the CNS or, in the other hand, an immune dysregulation (such as innate immune activation deficiency) makes these patients more susceptible to infections, and subsequent latent inflammation.[38–41]

A significant relation between TS and co-occurrent allergies seems to exist, once symptom exacerbation of some patients is seasonal and associated with food allergens, and both pathologies' courses have similarities.[42]

2.4. Stress

Psychosocial stress also exacerbates symptoms due to its neuroendocrinological effects. Now, it seems that stress and immunology might have a shared mechanism in TS pathology; stress perception leads to corticotropin-releasing hormone release, activating the hypothalamic–pituitary–adrenal (HPA) axis. It influences dopaminergic and adrenergic systems (namely the striatum-thalamus-cortical pathways) which are related to tics and other symptoms production, worsening stress. The immune system may also be related to the increase of dopamine in the CNS by the action of antineural antibodies, but a peripheric pro-inflammatory state mediated by dopamine is avoided by the HPA axis release or cortisol. These findings in TS patients agree with studies of different conditions such as OCD and Sydenham Chorea.[43,44]

3. Pathophysiology

Although yet far from a complete explanation, different neural pathways have been proposed to explain tics, premonitory urges, tic suppression and behavioural symptoms/comorbidities.

3.1. Tics

The motor output arises from the primary motor cortex due to internal or external inputs. The first appears from an interaction between prefrontal cortex, supplementary motor area (SMA) and basal ganglia (BG), while the second normally arises from the parietal-premotor circuit. Both systems seem to be altered in TS, once the parietal-premotor circuit is associated with echophenomena (caused by impairment in mirror neuron system inhibition) and the context-independency of tics is more associated with the cortico-basal ganglia-thalamus-cortical network (CBGTC).[11,45] So, symptoms result from physiological, morphological, metabolic and functional impairment in the homeostasis of inhibitory and excitatory circuits, mainly in the CBGTC circuit. Interestingly, due to scarce conclusive studies, most of these models were first proposed according to medication response.[7,46,47]

The CBGTC network (summarized in figure1) has a role in motor, cognitive, emotional, adaptation, learning and memory functions, as well as in action starting and translation of goal-directed into automatic actions. It consists of a bunch of circuits with somatotopy, which means that each functional part of the cortex has a specific projection into the BG, thalamus and cortex again. Of notice, there are three cortical afferent loops into the BG: sensorimotor, associative (from the prefrontal cortex and SMA) and limbic (from the orbitofrontal and anterior cingulum). These circuits are interconnected, which allows goal-oriented behaviour and its transition into habit formation (automatic actions) through reinforcement learning. The ventromedial prefrontal cortex-caudate nucleus circuit is related to goal-directed behaviours while the premotor/SMA-putamen circuit is related to habitual actions. For this last mechanism, the effect of dopamine is necessary through the *subtantia nigra pars compacta (SNc)*. The organization of this circuit in the hyperdirect, direct and indirect pathway allows the precise actions' structuration, permitting wanted actions (direct pathway) and blocking unwarranted competing motor programs (indirect and hyperdirect).[47–49]

So, the involvement of the CBGTC network (and therefore dopamine) in TS seems clear but its molecular mechanism does not. Four possibilities were postulated:

a)hypersensitivity of receptors

b)overaction of dopamine transporters, diminishing tonic and increasing phasic dopamine

c)presynaptic impairment

d)striatum DA hyperinnervation, and subsequent hyperdopaminergia

The only hypothesis that seems to explain all the TS phenomena is the dopaminergic hyperinnervation theory: excess of dopamine activates the direct pathway more than the indirect, which would increase both tonic and phasic dopamine, explaining both tic generation and learning, respectively. It is consistent with the recent suggestion that the dopamine active transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) increase in TS, as well as with the fact that drugs used in TS reduce both or one of the dopamine's forms. An increased number of dopamine receptors in the prefrontal cortex and striatum, especially D2 receptors, also seems to exist. Physiological oscillations in the dopamine circuit through life might also explain the clinical course of TS.[50–52] In the other hand, we should consider GABA, the principal inhibitory neurotransmitter in the central nervous system (CNS). Some studies have pointed the impairment in GABA circuits, namely modifications in $GABA_A$ receptors, and the diminish of GABA interneurons in the striatum.[46] The increase of glutamate in habit-related pathways and the role of histamine in striatum modulation was also suggested.[49,53] The autonomic nervous system was also hypothesized to have a role in CBGTC pathway regulation, with its impairment causing tics.[54]

What is more accepted in TS nowadays, is that tics occur through associative learning. It mostly happens due to impairment in dopamine and GABA circuits, causing inappropriate BG and cortical action (specifically of the prefrontal cortex and the motor preparation regions: SMA and premotor cortex). It leads to motor and limbic areas hyperactivation due to insufficient BG inhibitory control, which impairs the selection of wanted behaviours rather than unwanted ones. This has implications in motor habit learning and subsequent wrong selection of contextualized actions due to repeated release of impulses after tic (negative reinforcement). Once acquired, these automatic behaviours could be hard to correct. So, tics (both simple and complex) and habits seem to have a similar mechanism.[46,47,55,56]

3.2. Premonitory urges (PU):

PU were first thought to have a common neurologic mechanism with tics, once they appear mostly at the same areas (somatotopic correlation), suggesting them as a result of somatosensorial impairment. However, nowadays, it is believed that the mechanism is more complex once the urging mechanism is not similar for every patient and some of them not even have it. It was hypothesized that PU might be a consequence of abnormal exteroception (altered sensitive information arriving from S1 and S2 cortex areas). A GABA reduction in the sensorimotor cortex was described but, in general, tests were contradictory. Another theory describes PU as interoceptive (somatic) and tic as the automatic response to it. Patients with greater interoceptive sensibility (perception) would tic more which is consistent with the notion that tic severity is related to urges. It seems that people with a better perception of other interoceptive signals, also have

better recognition of PU. Some PET and fMRI studies have shown activation of the somatosensory and limbic areas (insula, parietal operculum and anterior cingulate cortex) before tics, associated with the sensation of urge. A relation between insula thinness and a deficient perception of urge was also postulated. The insula is the area where sensory, emotional and visceral information are integrated, and their input to the motor cortex is regulated by CBGTC network. So, it is speculated that the repetitive integration of PU because of somatosensory and insular cortices impaired inputs, leads to tic learning due to modulation of phasic dopamine circuits, moving from goal-directed actions into habits. It is not yet understood if some patients don't present urges or if they are simply not aware of that. There are also small series descriptions of other sensory phenomena such as visual impairment, namely in visual fields, colour vision and perception of complex visual stimuli.[14,55,57–59]

3.3. Tic suppression

Generally, symptom's severity decreases with age, totally remitting in some patients. Sometimes, they persist but patients can control them. Once these control and suppression are not general, they might be acquired. Tic control has a volitional component (once patients can control tics on demand, which requests active effort) and improves with age (possibly due to learning). Tics seem to be the only hyperkinetic disorder that can be completely voluntary inhibited. This mechanism involves the prefrontal cortex, is more effective in the muscle groups associated with less severe tics and seems to be internally and externally triggered. A passive form of tic control is also considered nowadays, as an effect of brain maturation. It is in line with the improvement of tic control with age, which could happen because of structural and functional compensatory brain modifications. These mechanisms seem to depend on cortical areas, especially the anterior cingulum, the SMA and the insula, and it might be related to the overactivation of specific GABAergic circuits that decrease motor excitability. The role of comorbidities in voluntary tic control is not well understood.[46,47,60,61]

3.4. Comorbidities

Both tics and OCS seem to result from changes in the CBGTC circuit, starting as goal-directed actions, then transformed into habits. However, tic disorders seem to be related to the sensorimotor striatum, while OCS seems to be a hyperactivation of the caudate, which agrees with the use of different targets on deep brain stimulation (DBS).[48]

ADHD has been associated with impaired dopamine, noradrenaline, acetylcholine, glutamate, opioids and serotonin circuits. These are involved in different functions (sensorimotor, cognition, attention and emotion). Some mechanisms might explain the comorbidity of TS and ADHD such as shared genetics and impaired microglial activation. Moreover, both pathologies seem to be related

to corticostriatal network activation errors and, although impairment in inhibitory control is present in simple TS patients, it seems to be worse in TS+ADHD patients.[14,62,63] The importance of prefrontal dysfunction and consecutive executive deficits in patients with comorbid ADHD and OCS was also evidenced, which hypothesizes the existence of a specific patients' cluster.[55]

3.5. New insights

Although all the research, TS mechanism remains unclear with lots of discoveries but not a total concordance between them. It is so far considered a movement disorder with deficient inhibitory control. However, from another perspective, it was recently conceptualized as a "surplus of action" rather than a deficient control, which is consistent with the idea of tics as overlearned responses (increased habit formation) to perception/sensory phenomena. So, it could be considered "a condition of altered perception-action binding" or "purposeful action". It is the basis of the "theory of event coding" (TEC), that postulates that both perception and action are encoded in a common mechanism. Consequently, the same sensation/perception that leads to a tic, may generate it again, even without being perceived (without PU). It is also accepted for eco, copro and impulsivity phenomena. This TEC model is in line with the postulated role of frontostriatal loops and BG in action selection, mediated by phasic dopamine. It is also related to the possible voluntary nature of tics, once they can be suppressed and tend to decrease while performing other activities and are associated with the SMA, which is related to voluntary movements.[52,64]

4. Patients' evaluation

It is important to access disease's impairment, which reflects quality of life through emotional, social, cognitive/occupational, and physical domains, taking different forms along lifespan.[65]

It is not clear if tics cause more impairment than non-tic symptoms, which seems to depend on age, activity and symptom's type and severity. For example, motor tics may disturb the patient during an exam, while phonic tics may be very limiting in social relations. With age, anxiety and depression become critical factors.[66]

Decreased self-esteem and perceived stigma (both frequent), are likely to result in social withdrawal. Learning disorders (eg.difficulties in mathematics, writing and speak) happens due to sleep disturbance, task delay because of motor tics, impairment of speech due to phonic tics and reduction of attention due to concentration in tic suppression. It happens mostly in patients with ADHD, probably due to impairment in concentration, social, and executive/fine motor skills. Adults seem to be less affected in jobs, but distressing school experiences may have consequences through life.[65,67(p2),68]

Depression has a great prevalence among TS patients, even in childhood/adolescence, that is directly related to the severity of tics, coexistence of other comorbidities, and familial history. It is important to access parent's mental health, once they are more prone to psychiatric morbidity as anxiety and depression, and it could be beneficial to refer them to mental health services.[69,70]

Suicide risk in TS patients is higher than in the general population, especially in those with comorbidities, and in adults with persistent symptoms. However, it should also be thought among youths, once even before adulthood some of them show, at least, suicidal ideation.[71,72]

Physical domain reflects direct consequences of tic intensity (eg.pain, injuries) in daily life activities.[65]

Despite all, most patients (particularly the eldest and those with more frequent tics) improve their quality of life through auto-coping strategies, especially tic suppression. However, some of them may experience post-suppression discomfort and difficulty in doing it on a daily-basis.[73,74]

To promote an accurate evaluation, many scales (the most recommended are summarized in table 3) have been applied, allowing an easier assessment of tics, associated phenomena and impairment. There are scales to be reported by the clinician, the informant or the patient.[7,75]

II. PATIENTS' MANAGEMENT

Besides all the recent investigation, the last consensus on TS treatment in Europe was published in 2011, by the European Society for the Study of Tourette Syndrome (ESSTS) in the European Clinical Guidelines for Tourette Syndrome and other tic disorders. So, an update on recent findings becomes relevant.

Four main steps in TS patients' management are followed: Psychosocial Intervention (PI), Behavioural Therapy (BT), Pharmacological Therapy (PT) and Brain Stimulation (BS).[67(p2)]

Fortunately, many cases are mild to moderate, and patients do not need treatment. In these cases, a "watch and wait strategy" may be tried along with PI, namely psychoeducation, before BT or PT.[67,76,77]

Treatment for tics could be initiated in cases of great impairment, namely in four situations:

a)Subjective discomfort (pain, injuries, migraine…)

b)Social problems (isolation, stigma, bullying)

c)Emotional problems (anxiety, depression, low self-esteem)

d)Functional problems (predominantly school impairment)

Comorbidities should be treated first if they are the main cause of impairment.

Notice that treatment mostly does not totally eradicate tics but truly reduces them.

The first evaluation and further treatment response may be evaluated through scales as the Yale Global Tic Severity Scale (YGTSS).[67(p2),76]

In this section, we will summarize the main features and recent findings in the different modalities of patients' management.

1. Psychosocial Intervention (PI)

It is important to ensure PI to every patient, family, educators and peers and to promote the link between them, once this has been proved to be essential to the efficacy of subsequent treatment. This is assured through psychoeducation, group work and charities/organizations. Psychoeducation (eg.supportive psychotherapy) gives support and information to understand the disease and comorbidities and avoid stigma. It also gives the patient coping skills to deal with tics and teach them how to improve social relations and to explain the disease to others. This approach is essential due to social anxiety that patients often feel, and they must be frequently re-evaluated. Group work allows a closer relationship between patients and parents in the learning of the disease, giving them support material.[76–78]

2. Behavioural Therapy (BT)

The past idea that BT could induce substitution/worsening of symptoms, is no longer considered. Moreover, it does not lead to the adverse effects of PT.[56,79,80] Studies comparing the efficacy of BT and PT are still lacking but it is suggested that they are comparable. So, BT is recommended as first-line therapy for most patients with mild to moderate tics.[81,82]

BT has two focus:

a)interrupting the negative reinforcement circuits involved in tic generation (through competing-response and/or exposure with response prevention)

b)changing the environmental and emotional factors that may trigger them (through avoidance and relaxation, since anxiety is an important tic prompt).

Some treatment modalities include more than one of this focus.[56,67,76] BT's limitations are tic severity and patients age; Patients with severe tics, can hardly suppress them for a long period and fail in concentrating in an urge at a time, which is necessary for the therapy. Evidence of success in patients younger than 10 years old has not been shown (maybe because they do not understand the treatment, they may not present PU or maybe just because of the scarcity of studies including youths). In which concerns to PT and comorbidities (mainly ADHD), its impact on BT is not consensual.[76,81,83] Patient's attendance to therapy is not always easy because of its price, the time spent and the lack of specialists.[76,80]

According to the European Guidelines, Habit Reversal Therapy (HRT) / Comprehensive Behaviour Intervention for Tics (CBIT) and Exposure and Response Prevention (ERT) are both recommended as first-line behaviour therapy for tics. They should be evaluated after 10 sessions, and if not working, they may be changed (one for the other) and then, PT should be tried. In severe cases, PT may be introduced first or together with BT and taken when the patient is stabilized. The choice between HRT/CBIT and ERT and the introduction of medication also depends on patients/parents will. As second-line BT, Contingency Management (CM)/ Functional Based Interventions (FBI) and Relaxation Treatment (RT) may be considered. Other therapies still lack evidence.[77]

2.1. Habit Reversal Therapy (HRT) / Comprehensive Behaviour Intervention for Tics (CBIT)

HRT is a complete treatment modality that associates tic antagonization, CM, motivation training, RT and behavioural approach. It beholds several stages:

a) awareness: patients learn how to identify tics, PU and external/internal triggers (through psychoeducation, diaries, videos)

b) competing-response: patients are taught to develop movements contrary to the tic (the use of the antagonist muscles of these used to tic were first described, but other authors consider any action that releases the tension). These movements may be practical and discrete, start

during the urge or after the tic has begun, and should last at least one minute or until the urge stops.

c) motivation: the impact of tics in the routine is evaluated and directly managed

d) generalization training: enforcement of those techniques in the daily life, to disrupt the negative reinforcement established by tic response to urges and consequent wrong habits.[56,76,78,84]

Since the first model, HRT has been modified and simplified, originating other treatment modalities. It is the case of CBIT, which principal component is HRT (mainly awareness and competing response - the active domains), but also others (eg.relaxation). It also includes psychoeducation and functional intervention (eg.CM) which allows targeting personal factors responsible for tics, managing it individually. In sum, CBIT is a development of HRT whose main purpose is to learn competing-responses to tics.[56,76,78,85–87]

CBIT has also been modified in models as CBIT-NP*,* trying to reduce therapy's duration, but they still have limitations.[88] Videoconference CBIT is already used in areas where there are no therapists and it seems to have similar results to face-to-face therapy.[56] Also, the website *TicHelper* available at *tichelper.com* tries to overrule the barrier of lack of professionals. It is based on CBIT manuals but easier to use. However, it is directed to tics and no other behavioural problems these patients might have, and it lacks the therapist feedback. Besides promising, its efficacy is not established yet.[85]

2.2. Exposure and Response Prevention (ERT)

Considering tics as a conditionate response to sensory phenomena, this therapy is based on the interruption between PU and tics, to reduce both. In therapy sessions, patients are supposed to bear PU (exposure) and avoid tic performance (response prevention) which will make them used to urges and to suppress tics in daily life (habituation). ERT was first used in OCD patients, once the reinforcement mechanisms of both pathologies are similar.[76,84,88]

Although HRT has more evidence base, both HRT and ERT have shown similar effects. Contrary to ERT, HRT seems to target only a few tics simultaneously, which might be worst in multiple tics patients. ERT is more applied by professionals, once it is also used in OCD. It would be preferred in patients with overt PU, while HRT may be advantageous if the patient does not present tics during the session, because contrarily to ERT, this may be taught during the session and trained later. ERT seemed to take double the time (two versus one hour) but this comparison was made based in groups with different treatment length, so it is not clear if ERT needs to be longer.[56,76,78] What is not clear yet, is whether habituation is established only between sessions or during it, and in that case, what would be the impact of reduced sessions in the habit formation. A recent study suggested no

difference in the efficacy of long and short ERT sessions. The best therapy length and session content are not established yet, once it varies between protocols and manuals, but it takes, on average, 10 weekly sessions.[84] It is suggested that a greater number of therapy sessions leads to better outcomes.[81] Other mechanisms of learning beyond habituation (eg.extinction) have been postulated.[84] One single small-sized study evaluated the possibility of combine HRT+ERT, but it did not show advantages.[89]

2.3. Contingency management (CM) / Function-Based Interventions (FBI)

CM consists of manipulating contextual factors, contributing to tic suppression. Tic-free moments are reinforced (eg.by tokens) while tics are ignored, which leads to tic reduction not by repression but due to the demonstrated positive effect of their suppression. FBI is a kind of CM based on specific factors. Both are used as part of other therapies such as HRT, and their effect alone is not assessed. A rebound effect after CM was proposed but not proved.[67(p3),78,90]

2.4. Stress Reduction and Awareness: Relaxation Training (RT), Self-monitoring (SM) and Mindfulness-based Stress Reduction (MBSR)

RT is very important in TS patients, once anxiety and stress are significant tic triggers. It is recommended as second-line or as a component of multiple treatments (eg.incorporated in HRT). It includes several techniques as stress reduction, muscle relaxation, breathing exercises and motor imagery. Hypnosis has not gathered enough proof of efficiency in TS yet.[78,91] SM, usually associated with HRT, also reduces tics. Patients are taught to immediately record the moment and situation in which tics occur. The benefit of RT and SM alone has not been proved yet.[77,78] MBSR improves awareness of emotions, thoughts and sensations, and increases attention and control, by reducing excitement. It showed positive results with tic reduction a month after the two-weeks therapy but in only one small-sample study.[92]

2.5. Cognitive Behavioural Treatment (CBT) / Cognitive Psychophysiological Treatment (CPT)

CBT is based on the concept of tics as regulators of sensorimotor functions once they release the tension of a muscle improperly contracted due to overpreparation (recruitment of unnecessary muscles) and overplanning (excessive effort). These muscles, even at rest, hardly reaches the “zero” tension level, which leads to chronic muscle tension in patients with tics.[87] This overaction happens not only due to hyperactivity and impulsivity but also perfectionism. So, CBT consists of a restructuration of patients' expectations that modify motor action and automatic planning.[86] It targets the system beyond thoughts and behaviours that leads to tics (anticipation, perfectionism, rigid beliefs, attention) and not the tic itself, and it is suggested to affect associated symptoms. Although the psychophysiological effects are not well understood, recent evidence suggests a modification of neural pathways after therapy.[93] However, due to the lack of studies in this theme,

it is left unclear if CBT's beneficial effect relies on relaxation and functional intervention or in the HR component, questioning the additional therapeutic value of CBT compared to HR.[78]

2.6. EEG Neurofeedback (NF) and Autonomic Modulation (AM): Bioneurofeedback (BF) and Vagus Nerve Stimulation (VNS)

These are based in operant conditioning: patients modulate specific neural networks, which allows positive reinforcement and self-neural-regulation.[54,94] In NF, a record of cortical activity through EEG is decomposed in frequencies and transmitted to a videogame (eg. racing car). Different frequencies of neural activity lead to different velocities and patients control it through feedback, regulating their neural frequency. NF targets mainly executive control (cognitive) functions (that are reduced due to impairment in the CBGTC circuits) and modifies this wrong cortical activation. In sum, it "re-calibrates" frontostriatal connections, improving cognition and attention. Once these functions are more impaired with comorbid ADHD, it might be more beneficial in these patients.[94] The increase of sympathetic tone as an excitatory afferent of the CBGTC led to the development of techniques that modulate it, namely BF and VNS, which together assemble AM.[54] BF consists of behavioural psychophysiological treatment. It focuses attention on body function (eg.muscle tension, breath), which promotes volitional control over implicit physiological responses by making it overt, through sensory feedback. Due to the role of the autonomic system in TS, it was suggested that electrodermal activity biofeedback (EDA) could reduce tics by psychophysiological brain modulation, reducing the sympathetic tone, with long-term effects.[54,95] Despite positive results, due to lack of studies, NF and AM are not yet recommended in TS.[54,94]

2.7. Tension Reduction

It consists of suppressing tics by recognizing an oncoming tic and transform it into another movement. It is usually used as a component of other therapies such as HR.[78]

2.8. Massed Negative Practice (MNP)

MNP was the first BT and it is based on reactive inhibition: tics are reduced through its voluntary rapid and repeated perform (eg.for 30 minutes). Its efficacy is contradictory, and it might even worse tics in anxious patients.[90]

3. Pharmacotherapy

Due to clinical variability and lack of big-series studies especially involving only children/adolescents, guidelines on PT are difficult to establish and consequently based not only in studies but also in experts' clinical experience. PT is recommended in the following situations:

a)after the failure of BT, with it or as single therapy

b)in patients who cannot access BT

c)as first-line or together with BT in very severe cases.[67]

Typical antipsychotics have more evidence-based recommendations. However, atypical antipsychotics are more in use due to their safer profile. Risperidone is the first-line PT proposed by the European Guideline.[67] Aripiprazole has recently been studied with positive results.[96] Benzamides are also in use and they are the first-line treatment in some countries like Germany. However, due to lack of studies, it is not the first-choice according to the European Guideline. α-agonists are not so efficient in reducing tics, but they could be the first-line treatment in patients with comorbid ADHD.[67] It is important to notice that these recommendations are not in line with what is preconized in the USA, where clonidine is the first-line therapy.[97] Selective serotonin reuptake inhibitors (SSRIs) have been the most prescribed drugs to depression, anxiety and OCS while stimulants have been the ones chosen in ADHD.[98] Besides all the recommendations, the use of certain drugs depends on the physician's experience, patients' needs and effectiveness of the drug in each patient. So, more than follow a specific guideline, it is important to choose the drug that best suits the patient, according to clinical presentation, tolerability, availability and preference. It is possible to move from a therapy to another in search of optimization, taking into account the patient and drug profile.[96,99] The most used drugs in TS are described below, and specificities of some of them are described in tables 5 and 6.

A. Pharmacological treatment of tics

3.1. Antidopaminergic agents

3.1.1. Antipsychotics

These are the most studied agents in TS. They are supposed to reduce tics by blocking the dopamine receptors, specifically D2, responsible for inhibiting the indirect pathway and therefore promote cortex excitation, blocking the overactivity of the CBGTC network.[99]

The main problem of antidopaminergics is their lateral effects. These are worst in typical antipsychotics but also happen with atypical antipsychotics, whereby follow-up of this patients is essential (namely metabolic, extrapyramidal symptoms (EPS) and cardiac monitorization, as well as dose control).[100,101]

3.1.1.1. Typical Antipsychotics

These drugs act not only in D2 but also in other receptors, depending on the agent. It leads to different side effects that conditionate their use, especially in high doses[67,96]

a) Haloperidol

Haloperidol was the first-line treatment in TS for many years. In its maximum doses, it can achieve 90% efficacy on tic reduction. However, due to its comparable effect with other drugs with fewer side-effects (mainly EPS), and lower administration doses, it is suggested nowadays in refractory cases.[97]

b) Pimozide

Pimozide has been suggested to have similar efficacy, better long-term outcome and less extrapyramidal effect than haloperidol but due to its calcium receptor blocker effect, it must be used with precaution in children and adolescents. Indications for the use of pimozide are like that of haloperidol. No recent studies have been performed on this drug.[96,97]

c) Fluphenazine

It was suggested to show good results and less lateral effects than haloperidol.[67] The only big series study performed on fluphenazine proposed that it could be effective in children and adolescents without permanent side-effects.[102]

3.1.1.2. Atypical antipsychotics

Due to having the same side effects as typical antipsychotics but with fewer EPS with same or better efficacy, atypical antipsychotics are nowadays preferred to haloperidol (the only drug regulated for TS in many countries). So, they are used off-label not only for tics, but also OCD/OCS, ADHD and other psychiatric comorbid disorders.[67,103]

a) Risperidone

It is the most prescribed drug in TS patients in Europe.[98] Its mechanism of action makes it good not only for tics but also for comorbid OCS.[96] It is the most studied drug in TS with proved efficacy, but no studies have been ruled recently. Moreover, its long-term side effects make its use not so linear. That is why, although its off-label use in Europe and the USA, it only has weak recommendation in Canada. So, even with good results, risperidone's administration must be well controlled.[67,97,103,104]

b) Aripiprazole

By the time of publication of the European Guideline, it was indicated as a promising treatment, however without significative evidence. Since then, research has been done, showing positive results. It was approved in the treatment of TS by the FDA in 2014.[105] It has also been prescribed as first-line in a specialized centre in the UK.[99] The great advantage of aripiprazole is its mechanism of action once it reduces the risk of EPS and anxiety.[96] Oral aripiprazole was considered well-tolerated, safe and effective, with the same effect as haloperidol and tiapride but much fewer lateral

effects.[106,107] Its safety and effectivity were confirmed by a recent double-blind placebo-control study that described sedation, and somnolence but no severe side-effects.[105]

c) Olanzapine, Quetiapine and Ziprasidone

Olanzapine's main problem is metabolic side effects. Besides the good results reported, no recent studies have been ruled on olanzapine and the current evidence is based on small series. So, it is not the first-choice treatment.[96,97] Quetiapine and ziprasidone have shown positive effects in reducing symptoms in small studies in the past and ziprasidone was even recommended in patients with obesity due to its low weight gain risk.[103] However, there are no recent studies on these drugs and studies of their use in other pathologies have shown side effects such as QT prolongation. So, they should not be used as first-line therapy, and monitorization is needed.[96]

In which concerns to newest atypical antipsychotics (iloperidone, asenapine, lurasidone, paliperidone, sertindole), evidence of its use in tics management have not been published yet (except some case reports on paliperidone).[67,96,103]

3.1.2. Benzamides

They have good tic response and fewer side effects than antipsychotics. In this group, the most recommended drugs are tiapride and sulpiride. Tiapride seems to have high selectivity for limbic areas, and sulpiride has low antipsychotic effect, as well as an antidepressant and anxiolytic effect in low doses. Once they are not available in the USA, they are not included in American clinical trials, but they are used and recommended in Europe based on clinical practice .[67,103]

3.1.3. Ecopipam

Based on a theoretical model where hyperdynamic dopamine pathways lead to hyperkinesia, both the direct (excitatory) and indirect (inhibitory) pathways might be involved. However, until now, only D2 receptor antagonists have been used in TS.[108] So, ecopipam, a high-affinity and selective D1 and D5 receptor antagonist has recently been studied.[97] Recently, it passed through a phase IIB trial in children and adolescents showing good results, with effectiveness and good-tolerance, without the side effects of D2 antagonists. The results were positive for motor and vocal tics, but no result was shown in mood disorders, ADHD and OCS.[108] This is in line with a small open trial performed in adults.[109] More information (eg.its effect on long-term follow-up) are needed to recommend it.[108,109]

3.1.4. VMAT2 inhibitors (dopamine depletors)

Benazines have already been tested in few patients with good results (but no placebo-controlled studies have been ruled).[110] Nowadays, valbenazine is in a phase II trial in the USA to be used in TS.[111]

3.2. Non-Dopaminergic Agents

Although the important role of dopamine in TS, it does not explain its association with comorbidities as anxiety, ADHD and OCD which leads to the possible intervention of other pathways. Besides not totally understood, that is supported by the effectiveness of non-dopaminergic agents.[97]

3.2.1. Alpha-agonists

Besides some controversy, clonidine and guanfacine were proved to reduce tics, although less than antidopaminergics, with a safer profile. Thus, they are recommended in TS, especially in cases of comorbid ADHD, due to their positive effect on attention.[112,113] One of the advantages of clonidine is its presentation as both oral and transdermal formulations.[67]

3.2.2. GABAergic drugs

Anticonvulsants as topiramate and levetiracetam have been proposed in case of failure of first-line treatments.[114,115] Baclofen is a $GABA_B$ receptor agonist, usually used as an antispasmodic, proved to be useful in motor and vocal tics, without severe side effects.[116] Although their use seems promising (especially avoiding antipsychotics' side effects), evidence-based recommendations are still lacking and some contradictory results are found in literature.[67,114–116] $GABA_A$ receptor agonists (benzodiazepines as clonazepam) have also been used in TS, but its use is limited by the common side effects.[115]

3.2.3. Anticholinergic drugs

3.2.3.1. Botulinum toxin A

Localized intramuscular injections are approved for many other pathologies and have been proposed to reduce vocal (including coprolalia) and simple motor tics, without systemic effects. It was also described as life-saving in patients with neck whiplash movements (dystonic tics). Small studies have found it efficient at short and long term, but due to lack of evidence it is still used off-label[117–119]

3.2.3.2. Mecamylamine

In the early 2000s, this nicotinic receptor blocker was studied in children and adolescents and showed good tic reduction, both combined with neuroleptics and in monotherapy. However, recent studies have not been conducted.[120]

3.2.4. Cannabinoids

Their use is still being studied. Evidence has shown a considerable effect of δ-9-THC (tetrahydrocannabinol) in the reduction of tics' severity and urges, and of CBD (cannabidiol) in anxiety.[121,121,122] They were also proposed to positively affect OCS, attention, impulsivity and self-harm.[123] In the paediatric population some case reports have shown the same results.[124] Cannabinoids are already recommended by some specialists in adult patients resistant to treatment. Despite all the new insights, they are based on small clinical trials and case reports using oral formulations of cannabinoids and smoked marijuana *(Cannabis Sativa).* Only a minority of evidence is based on controlled trials, but their results support the uncontrolled reports' conclusions. However, it is not yet enough to consider it a recommended treatment.[121–123,125]

3.2.5. Immunotherapy

Due to the putative immune aetiology of TS, the use of immunotherapy was postulated. Plasmapheresis, intravenous immunoglobulins (IVIG), antibiotic prophylaxis, tonsillectomy and anti-inflammatory drugs were tested in patients with criteria for PANDAS, PANS, CANS, and PITAND. Some of these treatments were also tested in patients with tic disorders and/or OCD. Though, these studies are scarce with inconsistent results.[67,126–128]

3.2.6. Traditional Chinese Medicine (TCM)

Some herb-based substances, particularly the 5-Ling granule and Ningdong granule, have been used in the TCM to treat tics. Their mechanisms might be related to the dopaminergic system and inflammatory processes' regulation.[96] Recent large randomized-controlled trials have proposed their efficacy, with one of them suggesting it to be as effective as tiapride.[129,130]

B. Pharmacological treatment of other symptoms and comorbidities

Not only tics cause impairment in TS patients. Giving medication for both tics and other symptoms should be avoided as a first-line treatment, which could be achieved through BT and PI. However, in some cases, drugs are necessary (even more than drugs for tics).[131]

According to the European Guideline, they should be used following the same algorithms as in patients without tics. In the case of important ADHD impairment, psychostimulants are preferred. They are effective and safe (though cardiac function must be accessed). Among them, methylphenidate has the greatest evidence-based recommendation. Long-action preparations are preferred. If tics are the main concern, α-2 agonists are preferred and may be conjugated with psychostimulants, and some authors consider they should be given before stimulants.[67,76] Disruptive behaviour disorder and aggressive behaviour also respond to this treatment.

Atomoxetine can also be used.[67,131] The use of antipsychotics, although not conclusive, may reduce the risk of impulsive behaviour.[21]

In TS+OCD/OCS, as in OCD only patients, BT as ERP is the first-line treatment. Ideally, PT should only be added in refractory cases, but due to the restricted access to BT, it is often used. SSRI are the most recommended drugs, with fluoxetine, fluvoxamine, escitalopram and sertraline approved in paediatric use, with similar effects. Clomipramine (a tricyclic antidepressant) has also been approved in this population, presumably with better effects than SSRI. Though, SSRI are preferred due to their safer profile. In refractory cases, a second SSRI, clomipramine or an atypical antipsychotic as risperidone may be added to the first SSRI.[76,131,132]

SSRI are also the first-line PT in cases of comorbid anxiety and depression. They should be used, if needed, as a complement to BT (especially RT) and PE. Regarding the drugs used in tic's management, benzamides, aripiprazole and cannabinoids also seem to reduce anxiety. It is necessary to the improvement of the tics themselves, and consequently, patients' well-being, minimizing depression states.[76,78,96,98,103,121]
Mecamylamine was also suggested as effective in mood instability and depression.[120]

Other drugs namely dopamine agonists (eg. pramipexole), antiemetics (metoclopramide, ondansetron), glucocorticoids, nicotine, Ω-3 fatty acids, IMAO blockers (deprenyl), NMDA agonists (riluzole, D-serine), antiandrogens (eg. flutamide) and lithium have also been referred in TS management. However, due to lack of evidence and recent studies, they were not described above.

4. Brain stimulation

When patients become refractory to BT and PT, neurostimulation may be tried. Three procedures are in the frontline of this approach: Deep Brain Stimulation (DBS), Transcranial direct current stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS).[116]

4.1. DBS

It consists of the placement of electrodes in specific brain structures, connected to an implanted pulse generator, providing high-frequency electrical stimulation.[133] The best target is still under discussion, but many structures have been tested, having on account the CBGTC dysfunction model: the medial thalamus [centro-median (cm), periventricular/ventralis-oralis (Voi) and parafascicular (Pf) nucleus], internal globus pallidus-GPi [anteromedial and posteroventrolateral], internal capsule's anterior limb (ALIC), the nucleus accumbens (NA) and subthalamus (specifically the H1 area of Forel's field). All of them belong to the ventral striatal-thalamus-cortical network. The thalamus (cm–Pf or cm-Voi) and GPi (AM-limbic or PVL-sensorimotor), has been the most targeted, showing better results, followed by the ALIC and NA. It is used bilateral stimulation at one target[134,135] Researchers are studying a multiple modulation possibility (motor, limbic and prefrontal-striatal networks), reaching both tics and behavioural symptoms, which has already been corroborated in a small study. It is hypothesized that thalamic stimulation would be better than Gpi's, in anxious, depressive or impulsive patients.[136,137] Moreover, striatum and subthalamic nucleus(STN) are already being targeted in patients with OCD. Also, long-term effects of DBS are being studied and it is suggested that GPi targeting could lead to a better outcome than the thalamic's.[138]

DBS is increasingly studied and used in adults, but evidence in paediatric patients is still little. The European Guidelines did not suggest this approach in children. This guideline advices for the use of DBS in adults are summarized in table 6.[134,138]

However, after that publication, the use of DBS in patients younger than 18 years has been suggested. The good results in treating paediatric dystonic patients with DBS led to try it in TS. The good outcomes (inclusively case reports of long-term follow-up), made experts consider that treatment-refractory patients should be evaluated multidisciplinarily (by neurologists, neurosurgeons, psychiatrists…), independently of being under 18. It might avoid irreparable damage or even death in youngsters with severe symptoms or malignant tics.[133,136,139] It is important, however, to realise some points; First, DBS can improve patients' condition, but tics might persist. Moreover, once brain develops through childhood/adolescence and only about 20%of patients keep symptomatic in adult age, evaluation of whose children/adolescents really would benefit is needed. Also, possible side effects as anxiety, dyskinesia, dysarthria, dizziness and

mood disturbances must be considered and may be minimized by parameters' adjustment. Surgical risks are minimal.[140] The main limitation of DBS seems to be its continuous delivery of stimuli, contrary to the natural fluctuating presentation of symptoms in TS. To solve that, a scheduled "intermittent stimulation" has been proposed, as well as adaptative DBS (aDBS), already used in Parkinson. It allows stimulation parameters' change according to clinical presentation, based in local neural activity (local field potentials-LFP), which provides "optimal moment-by-moment stimulation".[133]

4.2. tDCS

It is mostly applied in depressive disorders, but also in OCD and ADHD, consisting in neuromodulation using constant low current, delivered to the cortex through external electrodes (anodes or cathodes), which changes the rest membrane potential.[141] Some case reports suggested its use in TS (targeting the SMA) but it might be a bias, once those patients had severe comorbidities, so the exact role of tDCS in tics is not yet proved. Besides the safety shown in the paediatric population with other pathologies, in TS it was only performed in adults. A pilot study to be used in adolescents have already been designed .[116,141,142]

4.3. TMS

It has the same propose as tDCS, but the intracranial electrical current is created by a fluctuating extracranial magnetic field, and anaesthesia is unnecessary. There are fewer side effects (eg.headache). It has been proposed in TS patients, targeting the SMA, but evidence is still lacking.[116,142]

Conclusions

Recently, a growing number of publications on TS have been conducted. Despite all the uncertainties, some progress has been achieved.

An overlap between symptoms of other pathologies (TS, OCD, ADHD, anxiety) exists, with genetic investigation being important to highlight a spectral relationship between them. The importance of immunological and neuronal studies has also been shown. Those findings might be important to understand this pathology, leading to more accurate treatment.

However, findings are sometimes not reproducible or even contradictory, maybe due to the small-sized series, methodologies, age, medications in use and comorbidities, which makes it hard to create a pathophysiological model.

Patients' management is nowadays based in three different modalities: PI, BT and PT, combined according to tic severity and comorbidities.

Brain stimulation is already suggested in the paediatric population in refractory cases.

It has been shown that comorbidities' treatment is as important as the management of tics themselves.

BT is recommended as first-line therapy with good results at long-term follow-up and PT should be added only if needed. Risperidone remains the most prescribed drug for tics in Europe but aripiprazole and benzamides are already been chosen, due to their proved good results. Other drugs seem promising, but more investigation is needed.

In Portugal, most patients receive PT at first. A paradigm change is needed, with the introduction of BT and multidisciplinary evaluation.

In every therapy, lack of evidence seems to be the major limitation, underlining the need for further investigation.

Figures and tables

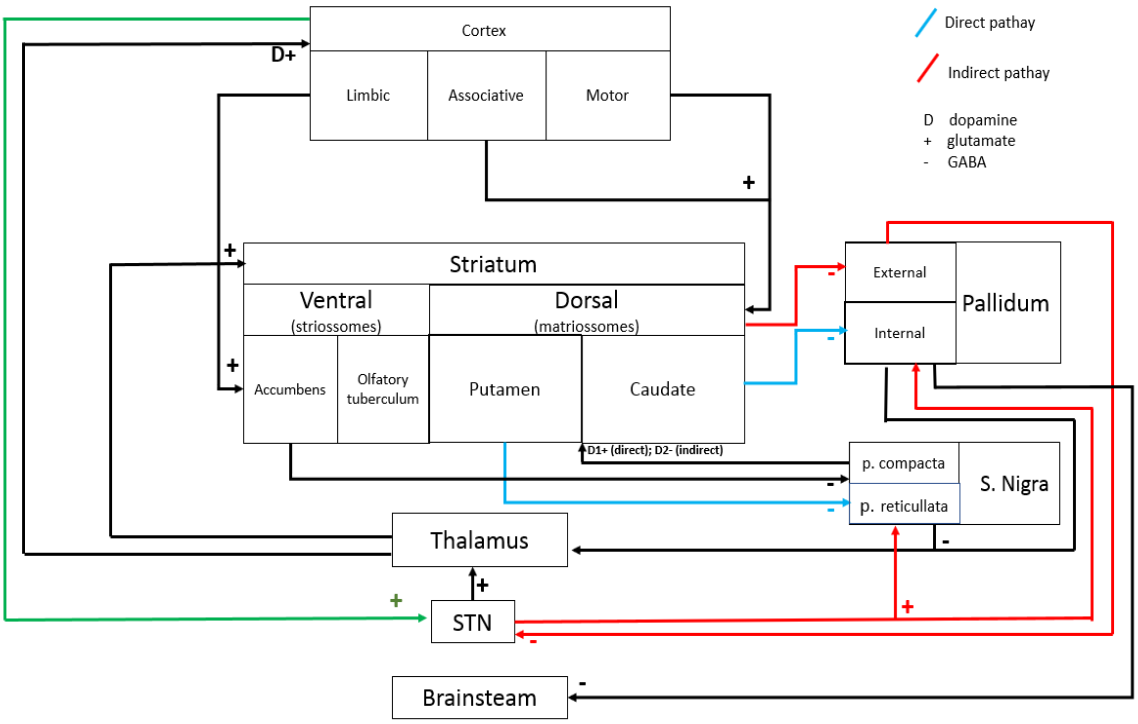

Figure 1- The cortico-basal ganglia-thalamus-cortical network (CBGTC)

Table I-The most recent diagnostic criteria for TS according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)

DSM-V criteria for the diagnosis of Gilles de la Tourette Syndrome[2]
• Both motor and phonic tics must exist at some point, but not obligatory at the same time; motor tics must be multiple, while phonic tics may be single or multiple
• Age of onset must be before 18 years old
• Tics may vary along with the presentation of the illness, but they must last for more than one year since their first onset
• TS diagnosis can only be made after ruling out other causes of tics such as substance consumption or other diseases

Table II- Differential diagnosis between tics and other movement disorders

	Tics	Stereotypies	Mannerims	Compulsions	Paroxysmal dyskinesias	Epileptic automatisms
Age at onset	Usually 5y	<2y	?	The same as tics	Any	Any
Pattern	Variable, wax and wane	Fixed patterned	Fixed	Variable	Fixed	Fixed
Movements	Proximal Complexity tends to increase	Distal, axial Complexity tend to diminish	All the topographies Complex movements	Complex	Dystonic or choreoathe-toid	Repetitive movement of eyelids, mouth, tongue or arms
Rhythm Duration	Rapid, sudden, random, intermittent and brief	Rhythmic, intermittent, prolonged	Non-rhythmic	Variable	Minutes	Minutes
Urges	Yes	?	No	Yes	No	No
Precipitant	Excitement and stress	Excitement and stress	?	Obsessive thoughts	Exercise	Usually none
Suppression	Briefly suppressible	With distraction, in the majority	Yes	?	No	No
Family history	Frequently positive	Maybe positive	Yes	Yes	Usually no	Usually no
Treatment	Clonidine Neuroleptics	Less responsive	None	SSRI	Antiepileptics	Antiepileptics

Modified from Mahone et al,2004[143]

Table III- Scales used in the evaluation of TS patients[7,75]

Scale	Features
Yale Global Tic Severity Scale (YGTSS)	-Evaluation of tics in all their dimensions (frequency, intensity, complexity and burden) -Identification of tics, exacerbations and response to treatment
Shapiro TS Severity Scale (STSSS)	Easier to use but less complete (not including for example frequency and complexity of tics)
TS-Clinical Global Impression (TS-CGI)	
Hopkins Motor and Vocal Tic Scale	Commonly used
Tourette's Disorder Scale	-Neuropsychological evaluation including intellectual and motor abilities, attention and memory in patients with comorbidities -Evaluation of comorbidities and behavioural symptoms
Swanson, Nolan and Pelham's questionnaire, 4th edition (SNAP-IV)	Evaluation of comorbid ADHD
Children's version of the Connors' ADHD Rating Scale for children (CAARS)	
Children's Yale-Brown Obsessive–Compulsive Scale (CY-BOCS)	Evaluation of OC symptoms Takes too long to be accessed
Obsessive–Compulsive Inventory-Child's Version (OCI-CV)	-Evaluation of OC symptoms -Briefer
Autism–Tics, ADHD, and other Co-morbidities inventory (A-TAC)	Diagnose of tic disorders
Major Scale Scores for Patients with Tourette's Syndrome (MOVES)	
Premonitory Urge for Tics Scale (PUTS)	-Evaluation of premonitory urges -After 10y

Table IV- Specificities of some drugs used in TS patients - part 1

Group		Drug	Mechanism of action	Side effects	Notes
Antipsycothics[96;144]	Typical	Haloperidol	• D2 antagonist • Muscarinic Ach antagonist • Adrenergic antagonist	• Highest prevalence of side effects: -EPS (tardive dyskinesia, akathisia, restlessness, parkinsonism) -malignant antipsychotic syndrome -hyperprolactinemia -weight gain -anxiety, depression, agitation, euphoria, insomnia, fatigue, irritability, confusion -headache -dry mouth, nausea -nightmares	
		Fluphenazine	• D2 and D1 antagonist	• Same as haloperidol but less prevalent	
		Pimozide	• D2 antagonist • Calcium-channel blocker	• Same as haloperidol but less prevalent • QT elongation	
	Atypical	Risperidone	• D2 antagonist (high dosis) • 5-HT2 antagonist (low dosis)	• Hyperprolactinemia and, at high dosis, EPS, in long-term use[103]	These drugs have been proved to have less EPS than typical antipsychotics, possibly due to their greater affinity for 5-HT2 receptors than for D2 receptors[103]
		Aripiprazole	• Partial agonism of the presynaptic and postsynaptic dopamine receptors, reducing dopamine synthesis and upregulation, but without completely block it: 5-HT2A antagonism (increases dopamine); 5-HT1A partial agonism (anxiolytic) • α - adrenergic antagonist[96]	• Same as typical but with much less EPS[96]	
		Olanzapine	• D1, D2, D3 and D4 antagonist • 5-HT2A and 5-HT2C antagonist • Muscarinic acetylcholine	• Same as typical but with less EPS • It is the atypical antipsychotic that causes the greatest weight gain[97]	
		Ziprazidone	• 5-HT1A, 5-HT2A, 5HT2C antagonist • D2 antagonist • α-adrenergic antagonist	• Transient somnolence • High risk of QT prolongation	
		Quetiapine	• D2 antagonist • 5-HT2 antagonist • 5-HT1A partial agonist • α1- adrenergic antagonist	• Metabolic and endocrine effects (hyperprolactinemia and hyperthyroidism) • Sedation, seizures • Tachycardia, QT prolongation	

Table V-Specificities of some drugs used in TS patients - part 2

Group	Drug		Mechanism of action	Side effects	Notes
Benzamides[96,144]	Tiapride		Selective D2 and D3 antagonist	• Weight gain, moderate increase of prolactin, nausea/vomiting, drowsiness, dizziness, anxiety, dry mouth, insomnia, headache, nocturnal enuresis • Lower sedation than haloperidol/ risperidone	
	Sulpride		Weaker, but highly selective antagonism of D2 receptors	• Hyperprolactinemia, weight gain • Less EPS than haloperidol	
VMAT2 Iinhibithors[110,111,144]	Tetrabenazine		Monoamine reuptake blockers (mainly dopamine)	• Depression • Parkinsonism, akathisia, dystonia (rare) • Sedation, somnolence, insomnia	• Seem to be as good as antipsychotics in hyperkinesias, with < side effects
	Deutetrabenazine		> half-life→ >concentration over the time with < doses and < peak concentrations	Less side effects	• Diminish pre-synaptic dopamine, with < risk of tardive dyskinesia than antipsychotics (post-synaptic action)
	Valbenazine				
α-agonists[97,112,144]	Clonidine		α -2 adrenergic receptor agonist	• Dry mouth • Sedation, fatigue, insomnia, irritability • Withdrawal reaction	Their mechanism in TS is not clear but it might be related with increase in noradrenaline outflow, which relates to specific cognitive and motor functions, more precisely in the STN supplementary motor loop, that has a role in inhibitory control and as such, in executive functions
	Guanfacine				
Ach-blocker[144]	Botulinum toxin A		Prevent Ach release at NMJ → temporary paralysis of the locally injected muscles, wakening it	• Asthenia, muscle weakness • Diplopia, blurred vision, ptosis • Dysphagia, hypo/dysphonia, dysarthria • Urinary incontinence • Breathing difficulties	
Cannabinoids	δ-9-THC and CBD		It is thought that the agonist effect of cannabinoids in CB1 receptor (concentrated in the BG, cerebellum and hippocampus) may inhibit glutamate release and therefore the excitatory input into the BG[123,144]		
Monoamine reuptake blockers used in ADHD	Psychostimulants[144]	Methylphenidate	Monoamine reuptake blockers	• Possible cardiac effects • Interference with tics in high doses[67,76]	
		Amphetamines			
	Nonstimulants	Atomexatine[131]	Nonstimulant selective NE reuptake inhibitor	• Sympathomimetic side effects • Risk of sedation	

Table VI-Advices for the use of DBS in adults according to the European Guidelines

Advices for the use of DBS in adults[134,145]
The diagnosis must be made by an experienced clinician
The technique must be performed at a reference centre
Tics must be the main symptom, causing true impact in the quality of life
Tics must be severe and refractory to treatment (resistance to three different drugs, including a typical and an atypical antipsychotic, and if available, only after 12 sessions of BT)
Comorbidities have already been treated according to specific guidelines
Major depression, suicidal tendencies and other disorders that interfere with the safety of the process must not be present by the time of treatment
Patients and their environment must be stable
Informed consent is necessary
The patient must be over 25 years old (acceptable also between 18 and 25), only after 5 continuous years of symptoms and after one year of severe symptoms: ≥ 35 in the YGTSS (in patients with history of severe symptoms but <35 in the YGTSS there is no consensus)
Psychotherapy must be recommended before and after the procedure to introduce the patient in a “life without tics”, reducing anxiety and depression

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