Gilles de la Tourette syndrome – A treatable condition?

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Gilles de la Tourette Syndrome – a treatable condition ?

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Abbreviations:
ACT - Acceptance and Commitment Therapy
ADHD – attention deficit hyperactivity disorder
BT – behavioural therapy
CBIT – Comprehensive Behavioral Intervention for Tics
CM/Pf – centromedian (CM)/parafascicular (Pf)-substantia periventricularis-nucleus
CNS – central nerevous system
DBS – deep brain stimulation
ERP – exposure response prevention
ESSTS – European Society for the Study of Tourette Syndrome
FAAH - fatty acid amide hydrolase
GABA - γ-aminobutyric acid
GPe – globus pallidus externus
GPi – globus pallidus internus
GTS – Gilles de la Tourette syndrome
HDC – histidine decarboxylase
HRT – habit reversal training
OCD – obsessive compulsive disorder
RCT – randomized controlled trial
STN – subthalamic nucleus
THC – tetrahydrocannabinol
TSA – Tourette Syndrome Association
YGTSS – Yale Global Tic Severity Scale

Abstract

Introduction: Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by chronic motor and vocal tics. Psychiatric comorbidity is frequent but does not enter into the official classification of the syndrome. In the present article, we will focus on treatment options for tics.

Methods: We have reviewed the relevant literature on treatment of tics and GTS, especially in the period from 2011-2016 since the publication of the European Society for the Study of Tourette Syndrome (ESSTS) treatment guidelines in 2011.

Results: We present current and up-to-date approaches in psychotherapy, pharmacotherapy and neurosurgery for GTS with an outlook for the upcoming years.

Conclusions: Although many patients and health-care professionals seem to view tics and/or GTS as difficult to treat, or believe that treatment requires severe side effects with reduction in quality of life, we wish to convey that there is cause for optimism, both with regard to available treatment modalities and future therapeutic developments.

Résumé

Introduction: Le syndrome Gilles de la Tourette (SGT) est un trouble neurodévelopmental caractérisé par la présence chronique de tics moteurs et vocaux. Les comorbidités psychiatriques sont fréquentes mais ne font pas partie de la définition officielle du SGT. Dans l'article présent, nous nous focaliserons sur les traitements anti-tics.

Méthodes: Nous avons analisé la littérature relevante concernant le traitement des tics et du SGT, en particulier couvrant la période de 2011-2016, c'est-à-dire depuis la publication des guidelines de traitement européens par la European Society for the Study of Tourette Syndrome (ESSTS) en 2011.

Résultats: Nous présentons les approches courantes sur les traitements anti-tics en psychothérapie, pharmacothérapie et neurochirurgie ainsi que les perspectives d'évolution dans ces domaines.

Conclusions: Malgré le fait que nombreux patients et professionnels de santé estiment le traitement des tics et/ou du SGT difficile, ou se focalisent sur les risques et effets secondaires potentiels, nous souhaitons mettre en avant un vision optimiste, aussi bien concernant le présent que les évolutions futures.

Introduction

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by the presence of at least two motor and one vocal tic over a period exceeding one year with onset before the age of 18 years [1]. Psychiatric comorbidities (attention deficit hyperactivity disorder, obsessive-compulsive disorder, autism-spectrum disorder, anxiety, depression and others) are multiple and occur in almost 90% of cases [2]. Nonetheless, tics remain the *conditio sine qua non* to diagnose GTS and are generally the reason individuals with tics seek to obtain a diagnosis and treatment. In this review, we will therefore focus on the treatment of tics. For those readers interested in the diagnosis and treatment of comorbidities, we refer to the textbook by Martino and Leckman [3] and a recent review series [4].

For several decades after Gilles de la Tourette's initial description [5], GTS was considered a psychogenic condition and therefore psychotherapeutic, especially psychodynamic approaches were used in trying to reduce tics [6]. In the early 1960s, haloperidol was introduced as a pharmacological agent for tics which also induced a paradigmatic shift, viewing tics primarily as abnormal movements with an organic/cerebral substrate [7]. However, the use of antipsychotics in non-psychotic patients remains a challenge to this day, ensuing a certain therapeutic scepticism if not nihilism both in the affected individual, their families, and their treating physicians. Also, beyond pharmacological approaches, more recent treatment options such as behavioural therapy (BT) and deep brain stimulation (DBS) remain unknown to many patients and health-care professionals [8].

In the present article, we will review major therapeutic advances in these three domains (BT, pharmacology, DBS) since the publication of the European Society for the

Study of Tourette Syndrome (ESSTS) treatment guidelines [9-12], thus covering mainly the period from 2011-2016, with an outlook for the upcoming years.

When and how do tics need to be treated ?

According to the ESSTS guidelines [10], four reasons should be considered for moving beyond giving psychoeducation to the patient and their system, and proactively treating tics:

1. Tics cause subjective discomfort (e.g. pain or injury)

2. Tics cause sustained social problems for the patient (e.g., social isolation or bullying)

3. Tics cause social and emotional problems for the patient (e.g., reactive depressive symptoms)

4. Tics cause functional interference (e.g., impairment of academic achievements)

As first-line treatment, we would nowadays – depending on availability and financial resources (psychotherapy not being reimbursed in all European countries) – advocate BT. The obvious advantage is the lack of pharmacologically-induced side effects. Also, these interventions provide the individual with a sense of accomplishment not obtained by taking drugs. Lastly, but speculatively, BT might affect the long term course of tic evolution by inducing plastic central nervous system (CNS) changes with a more favourable long term prognosis. Or at least, BT offers the paediatric patient the opportunity to develop a set of skills to cope and live with vocal and motor tics potentially for a decade or more. A second choice of intervention would be pharmacological treatment, either systemic (drugs per os) or local (botulinum toxin), either as stand-alone treatments or as add-on to BT. Lastly, DBS is reserved for patients either refractory to the aforementioned treatment options or responsive but burdened with severe medication-induced side effects.

Psychotherapy

There have been more than 40 years of research evaluating behavioural treatment for individuals with tic disorders. Most of the early research focused on tic control whereas more recently outcome measures encompass psychosocial wellbeing and daily function given that even the most potent interventions result in only modest tic reduction. In general, the evidence for BT is comparable to the most effective pharmacotherapy treatments [13]. There has been development in the emergence of psychological treatments which are effective, even if the underlying mechanism still remains elusive. Since the European guidelines describing best practice for BT were published [11] there have been developments in the delivery of treatment rather than any drastically new form of treatment.

Behavioural therapy

All treatments continue to recognise the inclusion of educational information about the aetiology, course, prognosis and commonly co-occurring conditions with GTS which is commonly a first step in the intervention.

Azrin and Nunn [14] developed a program referred to as Habit Reversal Training (HRT) which requires the individual to develop an awareness of a specific tic through tuning in to what is referred to as "premonitory urge", a sensory experience that signals the onset of a tic. In treatment, the individual learns to inhibit the production of the tic when they notice the premonitory urge by applying an incompatible movement or breathing pattern which they must hold until the urge to tic disappears. These tic-blocking behaviours are called 'competing responses'. The technique is taught to a point that it is used automatically so that the individual is able to carry out everyday tasks while they manage the tics and associated urges. Recently, randomised controlled trials (RCTs) have demonstrated significant improvement in tic symptoms following a course of HRT delivered as part of a wider

program referred to as Comprehensive Behavioral Intervention for Tics (CBIT) with moderate effect sizes in reduction in tics in children [15] and adults [16] post treatment.

Exposure and Response Prevention (ERP) is a similar BT, although less researched, has shown to have good efficacy in tic management in children and adults [17]. In ERP, the individual tolerates exposure to the premonitory urge that precedes the tic whilst suppressing the tic for as long as possible, the time of which is extended during and beyond treatment. The urge is emphasised through the course of treatment. The approach promotes habituation to the urge, reducing the subjective intensity of the premonitory urge. There has been some discussion recently in the literature as to whether the underlying mechanism behind the tolerance of the urge relates to habituation to the sensation or to challenge the belief that the urge and associated tic are locked into a negative reinforcement cycle. Treatment effects of ERP have been found to be comparable to that of HRT (Verdellen et al., 2004) in a small study of adults and children with GTS.

Cognitive-behavioural therapy

During the 2000s, BT has been extended to include cognitive elements of treatment in which the individual with GTS learns to restructure or reframe negative perceptions associated with tics, particularly in high risk situation [18-20]. Another treatment program 'Living With Tics' [21,22], which employs a modular approach, based on the individual's presenting problem has been evaluated in a small sample and found to show some promise with regards to impairment ratings and anxiety symptoms. The intervention employs cognitive restructuring tools alongside HRT to address distorted beliefs about having tics and the impact the negative thoughts have on the individual's everyday life with the aim of improving quality of life and reducing impairment associated with tics [22].

Third wave

Following the addition of the cognitive elements to BT, has emerged a group of treatments often referred to as "Third wave psychotherapy", an approach which emphasises emotions, mindfulness, dialectics, metacognition, acceptance and spirituality [23]. These developments are in their infancy in the treatment of GTS and to date have been cautiously coupled with HRT and show little demonstrable advantage on tic management. Reese et al. [24] assessed the feasibility of a mindfulness-based stress reduction treatment (MBSR-tics) targeting tic-related anxiety and frustration in a small group of adults with GTS. Results show improvement in severity and impairment. Another program used a program of adapted HRT which included Acceptance and Commitment Therapy (ACT) to promote acceptance of tic-related urges [25] in a small group of adolescents.

Despite the evidence-base for behavioural interventions, treatment is not widely available or accessible [22]. This lack of provision has been attributed to a limited awareness and few trained clinicians. To address the limitations of services, several novel treatment delivery approaches have been developed. The simple rules based, highly structured nature of BT has facilitated its adaptation for novel treatment delivery using approaches such as telemedicine [26,27], group treatment, and intensive outpatient treatment rather than traditional weekly sessions. In addition, there has been delivery of treatment by non-psychologist professionals such as occupational therapists [28], physicians and nurse practitioners [29].

Taken together, the evidence base for BT is fair but there is much room for development. Future research should aim for large, high quality, well designed studies with active comparison conditions, given the waxing and waxing of tics. Limitations to the evidence-base are that existing studies have been recruited in North America, Europe and recently Japan. Outcome measures have slowly started to include a broader remit beyond tic

severity such as psychosocial function and child-report of quality of life. Many of the studies to date are small pilot or feasibility studies with little replication. Importantly, it will be important to refine and understand the key active mechanisms of change within GTS treatment. Assessment of long term outcome following psychological intervention is not well documented in the literature and offers further potential for understanding the effectiveness of treatment.

Pharmacology

Antipsychotics

Antipsychotics, e.g. dopamine receptor antagonists (especially D2 blockers) have been the mainstay in the treatment of tics for half a century now, but with a considerable and ongoing reluctance. Clinicians using these drugs are especially afraid of extrapyramidal side effects, e.g. tardive dyskinesias. Therefore, in North America, first-line pharmacologic treatment of tics remains focussed on clonidine, an alpha-2-receptor agonist, or tetrabenazine, a presynaptic dopamine depletor [30]. European clinicians have a different stance on the subject as reviewed by Rickards et al. [31], favouring antipsychotics as first line treatment of tics, but with moderate enthusiasm nonetheless. Of note, a recent case review [32] on 521 adult GTS patients treated with antipsychotics supports the notion that they are not prone to tardive dyskinesia but seem rather "protected" against those, which, in our experience, also seems to hold true for paediatric patients. In general, antipsychotic dosages used to treat tics are much lower than treatment for psychotic patients. In practice, we feel that if tics require treatment, the most effective treatment should be offered first line, e.g. antipsychotics, whereas nondopaminergic drugs should rather be used as second line or add-on treatments [33]. Of note, alpha-2-receptor agonists are effective on tics only in patients with GTS and co-morbid ADHD [34].

Among antipsychotics, the best evidence is still available for haloperidol, pimozide and risperidone. In certain countries, benzamides such as tiapride and sulpiride are also frequently employed, based on the premise that they cause less sedation and weight gain than typical antipsychotics. Over the last decade though, aripiprazole has become the drug of choice both in pediatric and adult patients with GTS [35]. Aripiprazole has a unique mechanism of action as it is a partial D2 and 5-HT(1A) receptor agonist and a 5-HT(2A) receptor antagonist. It is considered a dopamine "stabilizer" as it displays an antagonistic action in the mesolimbic pathway but an antagonistic action in the mesocortical pathway, thereby normalizing dopaminergic transmission regardless of the type of imbalance [36]. In clinical practice, it is highly effective in reducing tics with lower rates of sedation and metabolic disturbances than typical antipsychotics. Recent studies in children and adolescents [37,38] have confirmed this clinical impression although we still recommend to check regularly, at least annually, for endocrine disturbances (note that aripiprazole decreases prolactine levels in contrast to other neuroleptics) and body mass index changes [39]. Also, based on personal experience, very low dosages ranging between 1.0-2.5 mg per day are often sufficient to control tics in children and even adults. For the latter, 5 mg per day is the usual dosage. Ramping this up to 10 or 15 mg daily sometimes helps but we do not observe a clear dose-response relationship in terms of therapeutic effects. In case aripiprazole does not offer adequate tic control, we usually first revert to typical (pimozide) or atypical (risperidone) antipsychotics or tetrabenazine (see above). An interesting alternative to tetrabenazine might emerge in the form of NBI-98854, a vesicular monoamine transporter 2 inhibitor already tested for the treatment of tardive dyskinesia and currently evaluated both in adult (ClinicalTrials.gov NCT02581865) and paediatric (ClinicalTrials.gov NCT02256475) patients with GTS.

Traditonally, antipsychotics used to treat tics block D2 receptors as they are mainly involved in the indirect pathway of the motor cortico-striatal-thalamo-cortical (CSTC) circuits. Comparatively, D3/D4 receptor blockers (olanzapine, clozapine, quietapine), more present in limbic portions of the CSTC circuits, appear of limited efficacy in treating tics. D1 receptor blockers have so far been unavailable to target the direct pathway of the motor CSTC circuits. Recently, however, an open-label trial investigating ecopipam, a selective D1 antagonist, has reported encouraging results in treating tics [40]. Consequently, a phase 2 randomized controlled trial using ecopipam has been registered and is currently recruiting paediatric GTS patients (ClinicalTrials.gov NCT02102698).

In case of partial but insufficient response to antipsychotics, another strategy involves adding a nondopaminergic drug, for instance levetiracetam, topiramate, clonazepam or baclofen. Among these, we favour topiramate as having the best evidence [41]. We will also mention the use of botulinum toxin, both in peripheral muscles for single, isolated tics, and in the vocal cords for disabling vocal tics as helpful stand alone of add-on treatment [42].

Cannabis

A strong candidate for tic reduction is cannabis, both based on clinical observations and studies performed in the early 2000s [43]. The availability of pharmaceutical grade cannabis products, especially tetrahydrocannabinol (THC) remains very limited but the situation might evolve over the next years, partly due to the introduction of cannabis-derived products to treat a variety of conditions such as spasticity, pain and appetite loss [44]. For instance, Sativex® (a buccal spray that contains THC and cannabidiol in a 1 :1 ratio) has recently been introduced in several European countries for the treatment of spasticity in multiple sclerosis and will likely be tested in large randomized clinical trials in patients with GTS in the foreseeable future (K. Müller-Vahl, personal communication). Another way to target the

cannabinoid system is to raise endocannabinoid (anandamide and 2-arachidonoyl glycerol) concentrations. An inhibitor of the main anandamide-metabolising enzyme, fatty acid amide hydrolase (FAAH) is currently being investigated in adult patients with GTS patients (ClinicalTrials.gov NCT02134080).

New targets

Overall, with regard to new pharmacologic treatments of tics, the past decade has seen little innovation except for the introduction of aripiprazole and the promises of THC. Nonetheless, the future appears brighter for patients with GTS than it used to be for two reasons. First, the recognition that GTS is not as rare as previously believed: recent meta-analyses point to a prevalence of 0.5% in the paediatric population [45]. As a consequence, both institutional and industry-driven research is picking up pace. Second, our understanding of GTS has deepened over the last decade, pointing to neurotransmission systems other than dopamine to be targeted. Among these feature most prominently acetylcholine, GABA, glutamate, and histamine.

Based on seminal postmortem work showing a loss of GABAergic and cholinergic interneurons in the striatum of patients with GTS [46,47] and possibly also in cortical areas, increasing GABAergic and cholinergic neurotransmission to treat tics is pathophysiologically plausible. Indeed, for GABA, both clonazepam and baclofen have been used in the past, with tangible but limited success so far [33]. Acetylcholinesterase inhibitors have also been tried in small cohorts and appear promising albeit for the fact that they seem to be poorly tolerated [48]. Nonetheless, individual dosages could be reduced by combining drugs to target several neurotransmitter systems simultanously [49]. Moreover, the development of better tolerated and/or safer (especially with regard to addiction) drugs is a distinct possibility. For instance, finasteride is a 5alpha-reductase inhibitor that received clinical approval for the treatment of

human benign prostatic hyperplasia and androgenetic alopecia. In the CNS, 5alpha-reductase is the enzyme catalysing the key rate-limiting step in the synthesis of pregnane and androstane neurosteroids. Accordingly, finasteride produces steroid metabolites with rapid non-genomic effects on brain function and behavior, primarily via an enhancement of GABA neurotransmission, with a plausible action on tic reduction in animal models of GTS [50] and a promising preliminary clinical study [51].

Glutamate as an excitatory neurotransmitter has also been declared a potential target for the treatment of tics although evidence for whether its action is increased or decreased in GTS is conflicting [52]. Therefore, studies aiming to either inhibit (riluzole) or stimulate (D-serine) glutamate neurotransmission have been initiated in children; first results were negative but the number of patients was small [53]. In the same vein, a trial with N-acetylcysteine, as an antioxidant and glutamate-modulating agent, has recently been completed although the results remain unpublished (ClinicalTrials.gov NCT01172288). Finally, a new formulation of acamprosate (SNC-102), usually used to treat alcohol addiction, is currently ongoing in adult GTS patients (ClinicalTrials.gov NCT02217007). Acamprosate is known to decrease brain glutamate, modulates N-methyl-d-aspartic acid receptor transmission and may have indirect affects on GABA-A receptor transmission.

The "new kid on the block" in GTS is histamine [54]. Deficiency in histidine decarboxylase (HDC), the rate limiting enzyme in histamine synthesis, has been implicated in familial forms of GTS [55,56] and animal models [57] have pointed to a relevant role of decreased histamine transmission in tic genesis. Pitolisant, a H3 reverse antagonist, is now being marketed for the treatment of narcolepsy [58] and has been tried once in a GTS patient [59]. This seems a promising candidate not only for tic reduction but also comorbid ADHD [60]. Two further H3 reverse antagonist are listed on ClinicalTrials.gov as undergoing or

having undergone clinical testing in GTS, AZD5213 (ClinicalTrials.gov NCT01904773) and PF-03654746 (ClinicalTrials.gov NCT01475383)

Surgery

Patient selection

Over the last 10 years, there has been increasing experience and experimental evidence of the efficacy and tolerability of functional neurosurgery, in particular of DBS, for individuals with GTS. In 2015 the International DBS Database and Registry Study Group endorsed by the Tourette Syndrome Association (TSA) of the USA has published an update on the recommendations for the treatment of GTS with DBS, including about 120 patients since 1999 worldwide [61]. Recommended selection criteria have been proposed (Box 1), which should include, amongst others, a DSM-5 diagnosis of GTS confirmed by a team of expert clinicians, high level of disability primarily caused by tics, a refractoriness to less invasive treatments, clinically stable psychiatric co-morbidities, and reliable social support to guarantee a safe post-operative monitoring. This study group also proposed a definition of refractoriness to conservative treatment which included a previous trial with three different classes of anti-tic medication (which should include one first and one second generation antipsychotic, as well as an α_{2A} adrenergic agonist), and at least the option of offering a course of behavioural therapy. In addition, a particular emphasis was given to the exclusion of patients with self- or heterodirected harmful ideation or possible psychogenicity, further supporting the importance of multidisciplinary evaluation of patients within a specialized team with longstanding experience in GTS [62], in which tics may cause bodily harm, e.g. 'whiplash' tics generating a risk of post-traumatic cervical myelopathy.

Update on evidence of efficacy

International guidelines on the preferable anatomical DBS target in GTS are still lacking, and the main reason for this limitation is the lack of active comparator trials. Approximately 80-85% of all patients with GTS with documented DBS were operated either on the centromedian (CM)/parafascicular (Pf)-substantia periventricularis-nucleus ventralis oralis internus crosspoint of the thalamus or the globus pallidus pars interna (GPi), with larger experience available when the antero-medial, or limbic, portion of the GPi is targeted.

The CM/Pf nuclei of the thalamus are the most explored target, with more than 70 cases reported. This nuclear complex influences motor and limbic circuits of the cortico-basal ganglia circuitry via a feed-forward mechanism that involves cholinergic striatal interneurons. Two randomized trials, one with parallel design [63] and one with cross-over design [64], both with a post-randomisation open-label phase, showed variable efficacy of bilateral CM/Pf stimulation across subjects but promising group differences pointing to a 37-50% improvement of tic severity that was sustained at follow-up. Results on the effect of comorbidities, recorded as secondary outcome measures, have been mixed.

The GPi is the main output station of the basal ganglia, hypothesized to be hypoactive in tic disorders. The largest to date randomized controlled trial targeting this region [65] was a crossover study that enrolled 13 patients, 11 stimulated in the limbic GPi and 2 in the motor GPi; each phase lasted 12 weeks and there was a post-randomisation open label phase. The mean proportional difference in YGTSS scores between the on-stim and off-stim conditions was 15.3%, corresponding to 12.4 points on the score. There were more consistent improvements during open-label stimulation adjustment. Progressive increase in amplitude of stimulation and number of active contacts was necessary over time, because suboptimum stimulation parameters were used in the blinded phase of the trial to guarantee masking. Interestingly, stimulation through the most dorsal contacts was associated with optimum tic

reduction, suggesting that stimulation of the globus pallidus externus (GPe) could also be involved. The largest open label series of limbic GPi stimulation came by Sachdev et al. [66] on 17 individuals followed up for a period ranging between 4 and 30 months; they observed tic reduction by 48-57% in 10 of them, and some collateral symptom reduction on obsessive-compulsive and depressive symptoms.

Amongst other targets documented in open label series, the anterior limb of the internal capsule and the nucleus accumbens have been used as targets for medically refractory obsessive-compulsive disorder, but in patients with GTS improvements have been very mixed, and mostly on the modest side. The group in Milan led by Servello and Porta used these targets as a 'rescue' procedure in patients whose tics improved with thalamic stimulation but were still troubled by obsessive-compulsive symptoms: interestingly, in almost all of these cases the rescue DBS did not objectively improve OCD but led to further improvements in their tic scores [67-69]. More research is needed on this target. Only isolated but positive experiences targeting the GPe [70] and the subthalamic nucleus (STN) [71] have been reported. The hypothesis of using the anterior STN or GPe as a potential target to treat the different manifestations of the complex GTS spectrum was suggested by data on the effect of this stimulation on the stereotyped behaviour of primate animal models [72].

Safety

DBS may lead to general, surgery-related complications that apply to all anatomical targets and indications, e.g. hemorrhage and infection of the electrode implant site. Whereas only a limited number of mechanical problems leading to breakage of lead connectors or wires (e.g. secondary to violent head tics) have been reported to date, the frequency of infectious complications (15-25% across series) at the level of the battery, extension cables or surgical wound raised some concerns [73]. Stimulation-related events associated with thalamic DBS in

GTS include sedation, abulia, fatigue, apathy, sexual dysfunction, and visual disturbances. Importantly, longitudinal observational studies showed that thalamic DBS may not lead to long-term adverse cognitive sequelae [74]. Anxiety with social avoidance, depression and hypomania have been reported slightly more with the GPi target, and overall resolved mainly with a course of pharmacological treatment. Dissociative and even psychotic symptoms have been exceptional occurrences, but threatening sufficiently to influence inclusion criteria and require very careful post-operative monitoring.

Future directions

Future research on DBS in GTS should first of all fulfill the need for active comparator trials. As patients with GTS may differ in response to treatment based on a particular comorbidity profile, larger, better powered trials would allow to adjust for the influence of comorbidities upon tic response to DBS. Although the crossover study design is by and large the most used, other designs, e.g. a delayed start design using blinded programming, might overcome the need to maintain stimulation parameters suboptimal in the blinded phase in order to guarantee masking [75]. With respect to outcome measures, existing trials showed that improvement of tic severity might not be paralleled by quality of life improvement. Databases and larger cohort studies would be crucial to assess long-term response, of which there is still very limited knowledge. The concept of closed loop DBS, which applies stimulation as a feedback to physiological changes (local field potentials at the target site, electric cortical activity, neurotransmitter concentrations), may be particularly suitable to the complex temporal dynamics of tics [76,77]. Finally, current directional steering by the use of the novel electrodes with a high number of contacts might improve the therapeutic window and help tailoring the treatment to the complex comorbidity profile of most patients with severe, medically refractory TS.

Conclusions

Today, clinicians treating patients with GTS have a wide range of treatment options, ranging from psychotherapy and pharmacotherapy to neurosurgery. It is also worth noting that these approaches can be combined depending on the patient's status and needs. A major problem remains the lack of large, well designed and controlled studies to assess different treatment modalities due to the supposed rareness of the disease. Also, as is the case in much of medicine now, endpoint definition is under intense discussion, e.g. should outcome focus on tic reduction, psychosocial function or quality of life measures [78] ? Finally, despite not being discussed here, the multiple psychiatric comorbities in individuals with GTS make evaluation and patient satisfaction a challenging but important task. Nonetheless, there is cause for optimism as public interest for GTS is increasing and patient organizations across the globe strongly advocate the development of more targeted, better-tolerated and safer therapies [79].

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BOX 1

Selection criteria for DBS [60]
- DSM-5 diagnosis of GTS by expert clinician
- Tic severity high (proposal: > 35 on Yale Global Tic Severity Scale, severity subscore) and tics prominent feature and cause of disability
- Tics refractory to conservative therapy (3 classes of medications + behavioural therapy)
- Stable and optimised treatment of medical, cognitive and behavioural comorbidities for 6 months
- Expected compliance during monitoring (stable psychosocial environment)
- Neuropsychological profile indicating that candidate can tolerate surgery, post-operative follow-up, and possibility of poor outcome
- Local ethics committee involvement for cases involving patients <18 years and for "urgent" cases