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**European clinical guidelines for Tourette Syndrome and other tic disorders. Part II:
Pharmacological treatment**

Veit Roessner¹, Kerstin J. Plessen², Aribert Rothenberger³, Andrea Ludolph⁴, Renata Rizzo⁵, Liselotte Skov⁶, Gerd Strand⁷, Jeremy Stern⁸, Cristiano Termine⁹, Pieter J. Hoekstra¹⁰ and the ESSTS Guidelines Group¹¹

¹ Department of Child and Adolescent Psychiatry, University of Dresden Medical School, Dresden, Germany

² Centre for Child and Adolescent Psychiatry at Bispebjerg, Capitol Region Psychiatry, Copenhagen, Denmark; Department of Neurology, Psychiatry and Sensory Sciences, Faculty of Health Sciences, University of Copenhagen, Denmark

³ Department of Child and Adolescent Psychiatry, University of Goettingen, Goettingen, Germany

⁴ Department of Child and Adolescent Psychiatry, University of Ulm, Germany

⁵ Renata Rizzo Child and Adolescent Neurology and Psychiatry, Maternal Infantile and Radiological Sciences Department, Catania University, Italy

⁶ Department of Pediatrics, Glostrup University Hospital, Copenhagen, Denmark

⁷ Norwegian Resource Center for AD/HD, Tourette Syndrome and Narcolepsy, Ullevål University Hospital, Oslo, Norway

⁸ St George's Hospital Neurology, London, UK

⁹ Child Neuropsychiatry Unit, Department of Experimental Medicine, University of Insubria, Varese, Italy

¹⁰ Department of Psychiatry, University Medical Center Groningen, University of Groningen, the Netherlands

¹¹ Members of the ESSTS Guidelines Group: Christos Androustos, Harald Aschauer, Gillian Baird, Netty Bos-Veneman, Ariana Brambilla, Francesco Cardona, Danielle Cath, Andrea Cavanna, Virginie Czernecki, Sandra Dehning, Alan Eapter, Luca Farkas, Julia Gadaros, Andreas Hartmann, Elizabeth Hauser, Isabel Heyman, Tammy Hedderly, Anne Korsgaard, Georgina Jackson, Linnea Larsson, Davide Martino, Claudia Menghetti, Nanette Mol Debes, Norbert Muller, Kirsten Muller-Vahl, Alexander Munchau, Tara Murphy, Richard Musil, Peter Nagy, Judith Nurnberger, Ben Oostra, Perry Paschou, Massimo Pasquini, Mauro Porta, Hugh Rickards, Renata Rizzo, Mary May Robertson, Domenico Servello, Jeremy Stern, Zsannett Tarnok, Jolande Van der Griendt, Cara Verdellen, Veerle Visser-Vandewalle, Ebba Wannag, Claudia Wenzel, Tomas Wolanczyk

Correspondence to:

Prof. Dr. Veit Roessner
Department of Child and Adolescent Psychiatry
University of Dresden Medical School
Fetscherstrasse 74

D-01307 Dresden

Germany

Phone: 0049 –351 458 – 2244

Fax: 0049 – 351 458 – 5754

Email: veit.roessner@uniklinikum-dresden.de

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Abstract

Objective: To develop a European Guideline on pharmacologic treatment (PT) of Tourette Syndrome (TS) the available literature was thoroughly screened and extensively discussed by a working group of the European Society for the Study of Tourette Syndrome (ESSTS).

Methods: Although there are much more studies on pharmacotherapy of TS than on behavioural treatment options, only a limited number of studies meets rigorous quality criteria. Therefore, we have devised a two stage approach. First, we present the highest level of evidence by reporting the findings of existing Cochrane reviews in this field. Then, we provide the first comprehensive overview of all reports on pharmacological treatment options for TS through a MEDLINE, PubMed, and EMBASE search for all studies that document the effect of pharmacological treatment of TS and other tic disorders between 1970 and November 2010.

Results: We present a summary of the current consensus on pharmacological treatment options for TS in Europe to guide the clinician in daily practice.

Conclusion: This summary is, however, rather a status quo of a clinically helpful but merely low evidence guideline, mainly driven by expert experience and opinion, since rigorous experimental studies are scarce.

Tic disorders including Tourette Syndrome (TS) are neuropsychiatric disorders with higher prevalence rates than previously thought, of up to 3-4% for chronic motor or vocal tic disorders and 1% (range: 0.05 – 3%) for TS [196], which is the combination of chronic motor and vocal tics persisting for at least one year. The typical age of onset of tics is four to eight years, and tics reach their peak severity early in the second decade of life often followed by a time of remission of tics [44, 228]. Overall, TS has often a favorable prognosis: follow-up studies of TS suggest that approximately one third of children with TS are essentially symptom free as adults; another third will have mild tics that do not require clinical attention [22]. Adults who still have symptoms severe enough to come to clinical attention are therefore unusual representatives of all subjects who have received a diagnosis of TS.

Diagnosing a tic disorder including the differentiation of tics from other movement disorders is usually a simple task (see Cath et al. this issue). It is, however, essential to detect coexisting conditions and to assess the contribution of the tics and/or coexisting conditions to the patient's psychosocial impairment in everyday life, because the coexisting conditions often are closely related to the latter, yet they do not explain fully the level of function [95].

1. Indications for treatment of TS

We use the term TS in these guidelines, although information also applies to other chronic tic disorders. Decisions about treatment of TS must be based on a thorough and broad diagnostic process. It is difficult to give guidelines with regard to indications for pharmacological treatment of TS, first, because persons with TS have a high interindividual variability of symptoms, secondly, due to the temporal fluctuations of tics and thirdly, because coexisting conditions may interfere with the treatment-effects for the tics. Moreover, subjective impairment does not necessarily equate objective tic severity: some individuals with relatively severe tics experience only mild impairment, whereas in other cases mild tics may be associated with significant suffering [225].

Many children and adolescents with TS do not require treatment for their tics, since their tics do not interfere with daily life or recreational activities. Indeed, only a minority of individuals with tics seek medical advice [194]. Many patients do well with a *watch and wait strategy* after psychoeducation and reassurance. Psychoeducation in TS has the aim to improve the tolerance for symptoms and to support stress reduction. Psychoeducation includes information about the long- and short-term variability of tics, about the natural course and about possible coexisting problems. A *watch and wait* strategy is also justified by the fact that we still lack evidence of the effect that pharmacological treatment of TS has on the natural long-term course and hence on the prognosis of the disorder and how this kind of treatment may influence the natural course of brain development. All pharmacological treatment options are therefore mere symptomatic treatment that alleviate, but do not cure the tics [87].

Non-pharmacologic and/or pharmacologic interventions should be considered in addition to psychoeducation for persons with clear impairment associated with the tics, either at first referral or later, due to exacerbation of symptoms. A number of reviews (e.g. [87, 246]) have published lists of indications for pharmacological treatment of tics, but none of them reflects the consensus of experts. We recommend that treatment of tics should be considered in the following circumstances, especially when persisting for some days.

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

Pain in TS may arise from the actual performance of frequent or intense tics causing discomfort by sudden or repeated extreme exertion (e.g. with head or neck). This kind of pain is usually musculoskeletal, although rare examples of neuropathic pain may occur. Tics can, in rare cases, cause injuries [125] e.g. a fracture line of both peroneal bones in a 13-year-old boy with TS and OCD admitted to hospital because of pain in his legs [80]. Striking or being struck by a moving body part involved in large amplitude tics may also cause pain and is

sometimes difficult to distinguish from deliberate self-injury. Additionally, some patients obtain relief from tics while experiencing pain, to such an extent that they will deliberately provoke pain to obtain benefit [193]. A smaller number of patients' complains of pain associated with the irresistible urge to tic or with aggravating premonitory urges during voluntary efforts to suppress their tics. Some patients report that tics worsen their headaches or migraines. Tic-suppressive medication may in those cases help to reduce the use of pain medication and should thus be considered.

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

Persistent complex motor tics and loud phonic tics can cause social problems. Tics may cause isolation, bullying, or social stigmatization; loud phonic tics may result in the child being put out of the classroom. In such cases a tic reduction, in addition to psychoeducation for the teacher, can be socially very helpful.

Tics do not lead to social impairments in all cases, however. Therefore, the issue of social problems needs to be assessed carefully. For example, parents of young children are often exceedingly worried about social problems, whereas adolescents sometimes overestimate the social consequences of their tics and children in the first elementary grades are often tolerant of tics. Coexisting conditions are more often the cause than tics, if a primary school child gets socially isolated by peers [54]. In higher schoolclasses bullying and social stigmatization due to tics becomes more common. After proper psychoeducation many children and adolescents will accept their tic symptoms and await the natural remission, however, sometimes medication is indicated to avoid social stigmatisation.

- *Tics cause social and emotinal problems for the patient (e.g. reactive depressive symptoms)*

In addition to the aforementioned sustained social problems as a consequence of negative reactions of the social environment some patients develop depressive and anxious symptoms, low self esteem and/or social withdrawal. In those cases it is not fully clear to

what extent coexisting (sub)clinical symptomatology and to what extent self-triggered reactions cause the patients social and emotional reactions to his or her tics.

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

Functional interference due to tics is relatively rare [87]. However, especially homework and falling asleep can be prolonged by bouts of tics and sleep may be disturbed followed by hypoarousal during the day. Frequent phonic tics can impair fluency of speech and thus conversations. Moreover, children can expend mental energy in the classroom to suppress their tics, thus reducing their attention to schoolwork and interfering with their academic performance [130].

2. Pharmacological treatment options for TS

Pharmacotherapy has probably the fastest onset and exerts the most prominent tic reduction when compared with behavioral treatment options. Although this clinical experience has never been tested in a clinical trial, it is possible to indirectly compare effect-sizes of pharmacological and non-pharmacological trials [19, 87, 132].

Genetic studies have so far not succeeded in pinpointing a clear deviation in the biochemical pathways in patients with TS. The existing models are mainly based on the efficacy of medication rather than on rigorous and replicable models. Findings from clinical medication studies, as well as from imaging studies and human material from blood, urine, cerebrospinal fluid and postmortem brain tissue analyses in rather small samples led to the common hypotheses on neurochemical deviances in TS [97]. Although evidence is appealing for deviances in the dopaminergic system, other imbalances, such as in the serotonergic, noradrenergic, glutamatergic, Gamma-aminobutyric acid (GABA)-ergic, cholinergic, and opioid metabolism in TS [97, 267] seems probable. Moreover, evidence grows that those systems play interactively together, especially the dopaminergic [263] and the serotonergic [160] system.

Studies supporting the strong hypothesis of an imbalance in the dopaminergic system have shown an increased number of striatal [285] and cortical [157, 290] dopamine receptors, as well as differences in binding to dopamine transporters in the basal ganglia [42, 233, 249, 286, 287] and release of dopamine following stimulant application [250]. Therefore, modulating the dopaminergic metabolism (particularly by blocking the post-synaptic D2-receptors) is the main action of drugs used in the pharmacologic treatment of tics.

Because only a limited number of studies on pharmacological treatment options for TS met rigorous quality criteria, we have devised a two stage approach. First, we present the highest level of evidence by reporting the findings of existing Cochrane reviews in this field. Then, we provide the first comprehensive overview of all reports on pharmacological treatment options for TS through a MEDLINE, PubMed, and EMBASE search for all studies that document the effect of pharmacological treatment of TS and other tic disorders between 1970 and November 2010. We found additional studies by going through references of each article. Given the scarcity of well-designed and well-powered studies, we think it is timely to provide such a complete overview of all available studies to present all facets of pharmacologic treatment accumulated over the last decades. Finally, we present a summary of the current consensus on pharmacological treatment options for TS in Europe to guide the clinician in daily practice. This summary is, however, rather a status quo combined with a clinically helpful but merely low evidence guideline and is mainly driven by expert experience and opinion, since rigorous experimental studies which would allow to better guide through well based clinical evidence are scarce.

We do not grade the studies with respect to their quality and include all available studies in view of the small base of evidence of pharmacological treatment options for TS. We present the existing studies for the different pharmacological agents, with respect to their

effects on tics and other accompanying symptoms and adverse reactions or interactions with other agents.

2.1 Cochrane Reviews

Although broad clinical experience guides the pharmacologic treatment of tics, the actual evidence based on randomized controlled trials (RCT) is alarmingly limited. Therefore, it is not surprising that all three existing Cochrane Reviews on the pharmacologic treatment of tics in TS [51, 186, 189] came to the same conclusion, i.e. that the evidence for efficacy and safety of the studied drugs does not allow firm recommendations.

Pringsheim et al. [189] included six randomized controlled trials on pimozide in TS (total 162 participants, age range 7 to 53 years). Pimozide was compared to placebo and haloperidol (two trials), placebo (one trial), haloperidol (one trial), and risperidone (two trials). In summary, the six studies showed that pimozide was more effective at reducing tics than placebo. It was slightly less effective than haloperidol, but showed fewer adverse reactions. The two studies that compared pimozide and risperidone revealed no important differences between these medicines for either reduction of tics or adverse reactions.

A more recent Cochrane review searched for all randomized, controlled, double-blind studies comparing atypical antipsychotics to placebo for the treatment of tics in TS [186]. It did, however, not include the two above-mentioned trials, because both studies compared the atypical agent risperidone to an active treatment without a control group receiving placebo medicine. Parallel group- and crossover studies of children or adults, at any dose and for any duration, were screened. Only three randomized placebo-controlled trials, two involving risperidone and one involving ziprasidone were thus identified. Risperidone was superior to placebo in one trial although the 95% confidence intervals were large. Two trials did not detect a statistically significant difference between treatment with risperidone and with

ziprasidone against placebo. Risperidone caused several extrapyramidal adverse reactions and weight gain.

The third Cochrane review on the pharmacological treatment of TS [51] analyzed the effect of Delta 9-tetrahydrocannabinol (Delta 9-THC). A total of 28 different patients included in one double-blind, crossover trial and in one double-blind, parallel-group trial were studied. Although both trials reported a positive effect of Delta 9-THC, the improvements in tic frequency and severity were small and only apparent on selected outcome measures.

In summary, all three available Cochrane reviews urgently advocate for future trials with longer durations and larger groups to investigate the safety and efficacy of pharmacological treatment in TS. Future trials should also use the Yale Global Tic Severity Scale (YGTSS) as primary outcome measure and standardized rating scales of adverse effects, e.g. the Extrapyramidal Symptom Rating Scale (ESRS).

2.2 Complete review

2.2.1 Antipsychotic agents

Positive effects for D2 dopamine receptor blockers have been reported in the treatment of tics since 40 years (in average a marked decrease of tics in about 70% of cases [237]). Particularly, the blockade of striatal D2 dopamine receptors is thought to lead to reduction of tics. However, a high blockade of the receptors correlates also with the rate of unfavorable adverse reactions, such as extrapyramidal symptoms (EPS) or tardive dyskinesia (TD) [27].

2.2.1.1 Typical antipsychotics

For a long time placebo-controlled treatment studies in TS have been conducted only to prove the efficacy of the typical antipsychotics *haloperidol* and *pimozide*. In an early randomized, double-blind, placebo-controlled cross-over study, both pimozide and haloperidol significantly decreased tic frequency in nine patients with TS [206]. The results of a subsequent randomized, double-blind, placebo-controlled study of the treatment of 57

patients with TS confirmed that both haloperidol and pimozide were more effective than placebo, but that haloperidol was slightly more effective than pimozide. Adverse reactions occurred more frequently with haloperidol versus placebo, but the frequency was not significantly different for haloperidol compared with pimozide [236]. The dosages used in this study ranged from 2 to 20 mg/day for haloperidol and from 2 to 48 mg/day for pimozide. The effect of the medicine with a strong blockade of D2 dopamine receptors reduced tics in up to 80% of the cases [236]. However, in daily clinical practice, lower doses such as 1–4 mg/day for haloperidol and 2–8 mg/day for pimozide are typically used nowadays to treat TS [128, 191, 224].

In a double-blind, 24-week, placebo-controlled, randomized double cross-over study of more commonly used doses of haloperidol (mean of 3.5 mg/day) and pimozide (mean of 3.4 mg/day) conducted with 22 subjects, aged 7-16 years, pimozide was significantly more effective than placebo in reducing tics, whereas haloperidol failed to have a significant effect. Moreover, haloperidol exhibited a threefold higher frequency of serious adverse reactions and significantly greater extrapyramidal symptoms relative to pimozide [214]. In contrast to several other studies, haloperidol was not superior to placebo, possibly due to the limited study power.

A long-term naturalistic follow-up study (1-15 years) of 33 patients with TS who were treated with pimozide (2-18 mg) or haloperidol (2-15 mg) also suggested benefits of pimozide over haloperidol: both drugs produced comparable relief of symptoms at follow up, but significantly more patients on haloperidol (eight of 17), compared with those on pimozide (one of 13), discontinued treatment [218]. Also, haloperidol produced significantly more acute dyskinesias/dystonias than pimozide.

A third typical antipsychotic, *fluphenazine*, has been used particularly in the United States for many years to treat TS, though it has merely been studied systematically. In an open-label study that included both children and adults fluphenazine was effective at doses

ranging from 2 to 15 mg/day in 17 of 21 patients [91]. In a naturalistic follow-up of 41 patients, treatment with fluphenazine for at least 1 year was safe and effective [240]. A small controlled study of fluphenazine, trifluoperazine, and haloperidol found similar reduction of tics. Fluphenazine was better tolerated, however [25]; haloperidol was associated with more sedation and extrapyramidal adverse reactions.

The high frequency of drowsiness and extrapyramidal-motoric adverse reactions (dystonia, akathisia, pseudoparkinsonism, probably due to the strong dopaminergic blockade in the nigrostriatal pathways) limits the use of the typical antipsychotics foremost in higher doses. It has also been reported that akathisia due to antipsychotic agents may worsen the tic symptoms [280]. Moreover, several case reports raised concerns about the risk of treatment with typical antipsychotics to induce tardive dyskinesia [93, 192, 241]. Although rates of tardive dyskinesia are difficult to quantify with confidence due to the few long-term data the risk of this potentially debilitating and treatment persistent adverse reaction should be a factor when considering choice of treatment [284]. This is of importance with even more certainty as atypical antipsychotics have shown a significantly lower risk of tardive dyskinesia [155].

Other adverse reactions e.g. the onset of anxiety [29, 138, 154] or hyperprolactinemia with its adverse reactions, such as gynecomastia, galactorrhea, irregular menses, and sexual dysfunction [205] are more common adverse reactions than tardive dyskinesia. Additionally, during long-term medication with haloperidol the increased appetite may result in significant weight gain [114].

2.2.1.2 Benzamides

The benzamides (*tiapride*, *sulpiride*, and *amisulpride*) are further selective D2 dopamine receptor antagonists but in contrast to the typical antipsychotics with low (sulpiride) or as good as no (tiapride) antipsychotic action.

In addition to tiapride's binding to supersensitive D2 dopamine receptors in the ventral striatum and parts of the limbic system (Locus coeruleus) a blockade of some serotonergic receptors (5HT3, 5HT4) is assumed. Since the 1970s there have been reports about successful treatment of TS with *tiapride* [61, 124, 139, 145, 183]. Several placebo-controlled studies on small sample sizes followed [43, 74]. Only one randomized, double-blind, placebo-controlled cross-over study has been published with tiapride (involving 17 children), indicating a significant reduction of tic symptomatology [68]. The main adverse reactions were drowsiness, moderate transient hyperprolactinemia, and weight gain (the maximum was 10 kg during 18 month in 2 children). Such massive weight gain is rather the exception than the rule, because the mean weight gain was 2–4 kg [151] with the dosage range of 100-900 mg/day. Tiapride had no adverse reactions on children's cognitive performance. Neither neurophysiological parameters such as the EEG frequency analysis and sensory evoked potentials were affected by tiapride nor were the neurosecretory, hypothalamic-hypophyseal regulation of the sex hormones, thyroid stimulating hormone, growth hormone, or thyroid hormone impaired. This rather advantageous profile of short- and long-term adverse reactions with doses effectively reducing tics has also been proven in rats [23, 227].

Since 1970 [291] positive effects on tics have also been reported regularly for the benzamide *sulpiride* [199]. It is a highly selective D2-Dopamine receptor antagonist associated with less extrapyramidal and vegetative adverse reactions than haloperidol [156]. An ongoing discussion focuses on whether that medication possibly has a specific binding in mesolimbic and mesocortical systems. In addition to its mild antipsychotic potency it has some antidepressant effect in low doses (in particular 50 to 200 mg daily) as well as a stimulating and anxiolytic effect [176]. In an open-label retrospective review in which 63 out of 114 patients (55%) suffering from TS had been treated with sulpiride [197], worthwhile beneficial effects occurred in 37 patients (59%). In a 14-week randomized, double-blind, placebo-controlled cross-over study trial of fluvoxamine (a specific 5HT reuptake inhibitor)

versus sulpiride followed by single-blind combined therapy (4 weeks) in 11 subjects with coexisting obsessive-compulsive disorder and TS [85], sulpiride monotherapy reduced tics and non-significantly improved obsessive-compulsive symptoms. Fluvoxamine, either alone or combined with sulpiride, non-significantly ameliorated tics and reduced obsessive-compulsive symptoms. Just recently in an open-label study with 189 children and adolescents with an average age of 8 years (range 3-15 years), 6 weeks' treatment with sulpiride improved motor as well as vocal tics. The most commonly encountered adverse reaction was sedation (reported by 16.4%) [100]. Also in patients suffering from OCD without tics sulpiride has proven its efficacy [14, 270]. In one case of treating TS with the combination of sulpiride and imipramine the tics increased [69]. This might be attributed most likely to the reported effects of increase of serotonin associated with increase of tics.

The main adverse reactions of sulpiride treatment are sustained sedation or drowsiness (up to 25%) and, less frequently, depression, despite its antidepressant, drive-normalizing, and mood-brightening potential [197]. Patients have also complained about restlessness and sleep disturbances [209]. Another important problem with sulpiride is a strong stimulation of prolactin-secretion causing galactorrhea/amenorrhea and a commonly observed increased appetite leading to weight gain [12, 105, 281]. Other adverse reactions occur less frequently (hypotension, rarely long-QT syndrome, dry mouth, sweating, nausea, activation or sedation, insomnia, allergic rash, or pruritus). There has only been one case report about tardive dyskinesia in an adult treated with sulpiride for tics (Eapen, Katona et al. 1993).

Successful treatment of TS disorder with *amisulpride* has been published only in case reports [75, 272].

2.2.1.3 Atypical antipsychotics

Atypical antipsychotics have also been found effective in the treatment of TS. The best evidence is available for risperidone. We will herein review all atypical antipsychotics in the order of their date of FDA-approval for non-TS disorders.

Clozapine, a dibenzodiazepine with 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, and weaker D₁ antagonist properties, and the first FDA-approved atypical antipsychotic agent (FDA-approval: 1990), has not been found to be helpful in the treatment of TS in several case reports which also documented the serious adverse reactions associated with this agent [35]. Rather, clozapine exacerbation of tics [13] as well as induction of stuttering, facial tics, and myoclonic seizures [15] has been reported.

The atypical antipsychotic agent best studied for the treatment of TS is *risperidone* (FDA-approval: 1993) with a high affinity for dopamine D₂- and 5-HT₂-receptors. In several case reports and open-label studies including small groups of patients risperidone showed similar efficacy in different ages as haloperidol and pimozide with, however, less frequent and less severe adverse reactions [30, 58, 86, 122, 140, 198, 219, 238, 261, 275]. The efficacy of risperidone has been confirmed in two randomized, double-blind, placebo-controlled trials involving 26 children and 8 adults with an age range of 6-62 years [226], and 48 adolescents and adults between 14-49 years, [60], respectively, with mean daily doses of about 2.5 mg (range 1-6 mg/day). Gaffney et al. subsequently [83] compared 8 weeks treatment effects of risperidone with clonidine in 21 subjects with TS aged 7 to 17 years in a randomized, double-blind study. Risperidone and clonidine appeared equally effective in the treatment of tics; however, in the cases with comorbid obsessive-compulsive symptoms, risperidone was superior. The most common adverse reaction seen with both treatments was mild to moderate sedation, which subsequently resolved with continued administration of the medication or with a dose reduction. No clinically significant extrapyramidal symptoms were observed.

Furthermore, in a 12-week, randomized, double-blind, parallel-group study both risperidone (26 patients were treated with a mean daily dose of 3.8 mg) and pimozide (24 patients were treated with a mean daily dose of 2.9 mg) reduced tics, anxiety, and depressive mood [28], whereas obsessive-compulsive symptoms improved only in the risperidone group. The latter finding is in line with the superior efficacy of risperidone for coexisting obsessive-compulsive symptoms in TS in the study of Gaffney et al [83] as well as in an earlier case report [86]. Although the severity of extrapyramidal adverse reactions was low in both groups, fewer patients in the risperidone group reported extrapyramidal adverse reactions (n=4) compared with the pimozide group (n=8). Depression, fatigue, and somnolence were reported as the most prominent adverse reactions in both treatment groups. This is in line with a retrospective study carried out in 58 adult and adolescent patients with TS who had been treated with risperidone. 17 (29.3%) patients developed a major depressive disorder, including one patient who later committed suicide and 13 patients (22.4%) became dysphoric while taking risperidone [143]. In contrast to the report of Bruggeman et al [28] suggesting equivalent efficacy of risperidone and pimozide in the treatment of TS, risperidone reduced tics more effectively than pimozide in a randomized, double-blind cross-over study involving 19 children aged 7 to 17 years with TS of 4 weeks of treatment with pimozide or risperidone followed by the alternate treatment after a 2-week placebo washout. Risperidone, however, was associated with more weight gain during the 4-week treatment periods. No serious adverse reactions were reported [88].

Risperidone also appears to be effective in treating aggressive behavior in patients with TS. In a retrospective chart review of 28 children and adolescents (one female) aged 5 to 18 years with TS and aggression problems, 22 (78.5%) showed both decreased aggression scores and tic reduction when treated with a mean daily dose of 2 mg risperidone [219]. This is in accordance with the potential of risperidone to manage pediatric aggression in other disorders [177]. Moreover, positive effects of risperidone not only on tics but also on sleep

disturbances have been reported in the case of a 12-year-old boy with no previous psychopharmacological treatment [7].

Finally, in line with other agents the problem of causality between treatment and the natural course of tic symptomatology has also been mentioned for risperidone leading to one report about induction of tics by risperidone [72].

Several case reports [17, 18, 117, 141] and open-label studies [33, 126, 148, 262] have suggested efficacy of *olanzapine* (FDA-approval: 1996) in the treatment of TS in adolescents and adults during the last 10-15 years. In four patients with severe TS (aged 19-40 years) a 52-week double-blind cross-over study with olanzapine (5 and 10 mg daily) vs. low-dose pimozide (2 and 4 mg daily) was performed [171]. The reduction in tic severity was highly significant with 10 mg olanzapine vs. baseline and vs. 2 mg pimozide, and was significant for 5 mg olanzapine vs. 4 mg pimozide. Only moderate sedation was reported by one patient during olanzapine treatment, whereas three patients complained of minor motor adverse reactions and sedation during pimozide treatment. All patients opted for olanzapine treatment at the end of the study. Compared to other antipsychotics, olanzapine has a greater activity at serotonin 5-HT₂ receptors than at D2 dopamine receptors. This may explain the lack of extrapyramidal effects. Additionally, olanzapine does not appear to block dopamine within the tubero-infundibular tract, explaining the lower incidence of hyperprolactinemia than with typical antipsychotic agents or risperidone. Nevertheless, the most widely reported adverse reactions were drowsiness/sedation and increased appetite frequently followed by weight gain [148]. In this context also metabolic adverse reactions (glucose and lipid metabolism) arise [184], although there seems to be no correlation between weight gain and metabolic disturbances [153].

Quetiapine (FDA-approval: 1997) with its greater affinity for 5-HT₂ receptors than for dopamine D2 receptors has shown its efficacy in reducing tics in two children with TS [179, 181, 182]. In an open-label trial with 12 subjects with a mean age of 11.4 +/- 2.4 years

quetiapine reduced tics significantly [159]. Three subjects complained of sedation in the first week of treatment, but in the 8 weeks under investigation patients did not experience extrapyramidal adverse reactions and no statistically significant weight gain. Contrarily, in a retrospective study with longer observation period and higher dosage (175.0 SD 116.8 mg/day) of quetiapine the only noteworthy adverse reaction was weight increase. Quetiapine reduced tics also significantly in an open label study of 12 patients aged 8-18 years with TS [48]. Routine laboratory parameters and serum prolactin level were all normal and did not change throughout treatment.

Although there has been great hope for *ziprasidone* (FDA-approval: 2001) as a potent treatment option in TS without the problem of weight gain [6], only one randomized, double-blind, placebo-controlled study in 28 children and adolescents (7-17 years) [212] and one open open-label study in 24 children and adolescents (7-16 years) so far has proved this expectation [211, 213]. A mean daily dose of 28.2 mg ziprasidone reduced tics more effectively than placebo. Mild transient somnolence was the most common adverse reaction of low-dose exposure (5-20 mg/day), consistent with what is seen in clinical practice. This, may be caused by enhanced 5-HT_{2C} antagonistic activity of ziprasidone at low doses [260]. No patient experienced extrapyramidal symptoms, akathisia, or tardive dyskinesia, although administration of a single, low dose of ziprasidone may not be reflective of either higher doses or long-term risk in a naturalistic treatment setting [213]. In addition, there was no weight gain and changes of the analyzed laboratory parameters except of prolactin. Although QT prolongation has been discussed prominently in ziprasidone, a single dose of ziprasidone to treat TS was well tolerated without clinically significant effects on electrocardiograms collected around the time of maximum serum concentration [213] and even in higher doses no elevated risk of QT prolongation has been reported compared to other antipsychotics [266].

In addition to ziprasidone also *aripiprazole* (FDA-approval: 2002) induced no weight gain during an 8-week, open-label trial with a flexible dosing strategy of aripiprazole in 72

children and adolescents with TS aged 6-18 years [49]. In a 10 week open-label, flexible-dose study with eleven subjects (10 males) with TS (age 9–19 years) who had not responded to or had not tolerated previous tic medication, effects of aripiprazole were promising [142], albeit with some weight gain in five patients. Finally, in an open-label, flexible-dose study including sixteen children (15 males) aged 8–17 years there was a mean increase of 2.3 kg after a 6-week trial with aripiprazole [167]. It provides a high affinity at dopamine D2 receptors but acts in contrast to other atypical antipsychotics as a partial agonist. Under treatment of clinical useful doses (10-30 mg/day) aripiprazole exhibits D2-receptor binding of 80-100% [96]. However, while binding at the active state of D2-receptors, aripiprazole shows 30% agonistic activity compared to dopamine [34]. Aripiprazole also acts as a partial agonist at 5-HT1A receptors and as a potent antagonist at 5-HT2A receptors [113]. This profile raised the hope that aripiprazole might be superior to previous pharmacological treatment options even in refractory cases. Excellent efficacy in the treatment of tics has been reported in a total of 201 cases, at least 31 of them adults [31, 47, 49, 52, 55, 63, 76, 103, 106, 118, 119, 142, 158, 166, 167, 173, 265, 288, 289]. A randomized, double-blind, placebo-controlled study is, however, still lacking. Nevertheless, this drug should be considered because of its promising perspective based on actual clinical experiences. Even in "refractory" TS, aripiprazole has shown about 75% reduction of severe coprolalia in a 28-year-old man [16] as well as good efficacy in treating TS and coexisting OCD in an adult female [283]. Accordingly, Budman et al. [32] found in their retrospective, observational study of 37 children and adolescents with TS who were refractory to previous treatment that aripiprazole still reduced tics as well as explosive outbursts in these patients. Aripiprazole was tolerated reasonably well, although 8/37 (22%) children discontinued treatment; most common adverse reactions included weight gain, akathisia, and sedation at a mean daily dose of 12.3 (SD 7.50) mg in the 29 subjects who completed the study. In a 12-week, open-label trial with flexible dosing strategy aripiprazole revealed a good tic reduction in 15 participants, aged 7-19 years. Nausea and sedation were

the most commonly reported adverse reactions that ameliorated in all participants within 2 weeks, with the exception of 1 participant who had continuously complained of sedation, but did not stop taking the drug [232]. The mean weight gain during this study was negligible.

For the newest atypical antipsychotic *paliperidone* (FDA-approval: 2006) as well as for *sertindole* (not approved by the FDA for use in the USA) no data on the treatment of tics have been published.

2.2.2 Noradrenergic agents

In general, noradrenergic agents (clonidine, guanfacine, and atomoxetine) are mostly used in children and adolescents with a combination of attention-deficit/hyperactivity disorder (ADHD) and mild tics given their efficacy in treating ADHD symptoms in addition to tics [11]. Their tic-suppressing effects seem to be generally smaller, however, than those of antipsychotic agents.

Despite the frequent use of the α -2 adrenergic agonist *clonidine* for nearly three decades in the treatment of TS, controlled studies with clonidine are few in number. It is used more commonly in America than in Europe [195]. Case reports of clonidine's efficacy in treating TS appeared in the early 1980s [150] and open-label trial evidence has been contradictory [45, 46, 234, 248]. A single-blind, placebo-controlled trial demonstrated a significant improvement in 6 out of 13 patients [133]. A randomized, placebo-controlled trial on 47 patients (7-48 years old) suffering from TS showed that treatment with clonidine reduced tic severity and frequency better than placebo [134], whereas another randomized, placebo-controlled study in 30 children and adults with TS found no difference [92]. A randomized, double-blind, placebo-controlled study of desipramine and clonidine for the treatment of ADHD in TS revealed that clonidine did not alter tic severity in 34 children aged 7-13 years [247]. However, in the largest well-designed, randomized trial on orally

administered clonidine, which included a placebo group, clonidine reduced tics significantly [271].

A transdermal clonidine preparation is also available and has been tested for the first time in nine patients in a placebo-controlled crossover trial. Although no objective improvement was recorded, most subjects felt they had improved [84]. A recent randomized, double-blind, placebo-controlled multicentre trial using a clonidine adhesive patch revealed in the randomly assigned clonidine group (n= 326) a significant improvement of TS in 68.85% compared to 46.85% in the clinical control group (n= 111) [62]. Accordingly, clonidine transdermal patch treatment was effective in 53 out of 65 children with TS [116].

Adverse reactions of clonidine include sedation, dry mouth, headache, irritability, and midsleep awakening [62]. Blood pressure and pulse should be measured at baseline and monitored during dose adjustment. Specific guidelines for blood pressure monitoring during follow up have not been established but regular monitoring of pulse and blood pressure changes, and symptoms suggestive of cardiovascular problems (e.g., exercise intolerance, dizziness, syncope) is recommended [53]. Baseline and follow-up electrocardiograms have been recommended in some practice guidelines [64], but not in others [53]. Although blood pressure is generally not a problem with clonidine, patients and families should be educated about the possibility of rebound hypertension, tics, and anxiety with abrupt discontinuation [19]. Although many authors report that the adverse reactions tend to be mild and transient, this view is not fully supported by others [89, 99, 137] especially when moderate to severe tics require higher dosage.

Guanfacine, another α -2 adrenergic agonist, has modest efficacy in reducing tics and in improving attention in children and adolescents. An open-label study of guanfacine in 10 children with TS [40] and in 25 medication-free children (23 males and 2 females) [24] with TS+ADHD aged 7 to 16 years revealed a significant decrease in tic severity and improvement in attention. Also, a case report had described a six-year old boy with TS treated successfully

with guanfacine [77]. These open label observations were confirmed by a randomized placebo-controlled double-blind trial in 34 children with TS+ADHD with a mean age of 10.4 years [223]. In contrast, in another double-blind, placebo-controlled study on 24 children with TS aged 6 to 16 years guanfacine was not superior to placebo [50]. In summary, whether guanfacine would be effective for the treatment of moderate to severe tics remains unanswered [225]. Also the suggestion that guanfacine is a better-tolerated alternative to clonidine remains unclear without a direct comparison study [217].

The most common adverse reactions of guanfacine are somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. Somnolence, sedation, and fatigue adverse reactions emerge within the first 2 weeks of dosing and generally remit [210]. There is a concern that guanfacine has a propensity to induce mania in children with a personal or family history of bipolar disorder [102] as well as syncopal episodes probably due to drug-induced hypotension or bradycardia [123]. Guanfacine approved to treat hypertension in several European countries has been withdrawn from the market in several European countries probably due to lack of financial success.

The selective noradrenaline reuptake inhibitor *atomoxetine* had already been shown to be effective in randomized, placebo-controlled trials for treating ADHD in children [41]. Also in the treatment of ADHD with coexisting tics its efficacy was tested in a large, industry-sponsored multicenter study in 148 children [5]. Atomoxetine reduced both tics and ADHD symptoms in the study's subgroup suffering from ADHD+TS [256]. Significant increases of mean pulse rate and rates of treatment-emergent nausea, decreased appetite, and decreased body weight were observed during medication with atomoxetine. Concerns were raised, however, that children with severe ADHD or tics might have been unlikely to be enrolled in the study [87] which had a fairly high dropout rate in both treated (34%) and untreated (26%) groups during the double-blind portion of the trial. Moreover, case studies describe patients

experiencing manifestation, recurrences, or exacerbation of tics following treatment with atomoxetine [136, 178, 180, 230].

2.2.3 Alternatives

Tetrabenazine, a vesicular monoamine transporter type 2 inhibitor, depletes presynaptic dopamine and serotonin stores and blocks postsynaptic dopamine receptors. In view of the hypothesized supersensitivity of dopaminergic receptors thought to be responsible for the tics in TS [231], tetrabenazine might be an alternative to antipsychotic treatment. Its divergent mechanism of action might result in different efficacy and adverse reactions profiles than the treatment with antipsychotics [109]. In some clinical studies on hyperkinetic movement disorders, including patients or samples with TS, tetrabenazine has shown its potential to ameliorate tics [108, 109, 111, 112, 174, 268, 278]. Results of two retrospective chart reviews enrolling only patients with TS (n = 77; mean age about 15 years; [120] and [188]) showed that 18-24 months' treatment with tetrabenazine resulted in a moderate to marked improvement in functioning and TS-related symptoms in over 80% of patients. Adverse reactions included drowsiness/fatigue (36.4%), nausea (10.4%), depression (9.1%), insomnia (7.8%), and akathisia/parkinsonism (6.5%), but these symptoms improved with reduction in dosage [120]. Weight gain was less pronounced in doses of comparable efficacy than under treatment with antipsychotics and most patients who switched from an antipsychotic drug to tetrabenazine subsequently lost weight [170]. There were no reports of tardive dystonia or serious adverse reactions. In contrast there is a report about two patients with TS who developed tardive dystonia after treatment with antipsychotic agents. The dystonic movements persisted after the offending drugs were stopped and improved with tetrabenazine [252]. In summary, these findings encourage to conduct further studies.

Findings from preclinical studies in animals have suggested that *nicotine* might potentiate the effect of antipsychotic agents used to treat TS. Indeed, in 2 case reports

negative effects of smoking cessation on TS have been reported [57, 59]. In initial open-label studies chewing nicotine gum in addition to treatment with antipsychotics reduced tics in frequency and severity and improved concentration and attention [146, 216]. Similar effects were observed in a subsequent controlled trial involving nicotine gum plus haloperidol. Only in the group chewing the nicotine gum tic frequency was reduced, while placebo gum alone had no effect on tic symptoms [147]. However, the short duration of effects as well as the bitter taste and gastrointestinal adverse reactions limit the compliance. Similar findings have been reported for application of transdermal nicotine patches to potentiate haloperidol in TS [242, 243]. In 11 poor-responders to antipsychotic treatment of TS, transdermal nicotine patches delivering 7 mg of nicotine in 24 hours reduced tics 47% in frequency and 34% in severity [244]. In 2 of these patients tic reduction lasted even after removal of the transdermal nicotine patches. This result was in line with similar reports on tic reduction longer than 4 weeks after 48 hours of nicotine administration by a transdermal patch [66, 67]. Correspondingly, retrospective case studies also found that application of a single transdermal nicotine patch delivering about 7 mg nicotine in 24 hours resulted in a significant tic reduction for a mean of 10 days [239, 243]. The participants complained, however, about nausea and occasional headache and sedation. In the first randomized, double-blind study 70 patients with TS were treated with either transdermal nicotine (7 mg/24 hours) or placebo patches in addition to their individual optimal dose of haloperidol [245]. In the patients who completed all 19 days of nicotine (N = 27) or placebo (N = 29), improvement of emotional and behavioral symptoms but also adverse reactions such as nausea and vomiting were more frequent under nicotine treatment. A subsequent randomized, double-blind, placebo-controlled trial examined the acute (4 h) and sustained (2 weeks) effects of a single dose of transdermal nicotine on clinical (i.e., tics), attentional (continuous performance task, event-related potential, patient and parental reports), and behavioral symptoms in 23 children and adolescents with TS receiving treatment with antipsychotic agents. In the 14 evaluable

patients with complete primary efficacy data, nicotine (compared to placebo) failed to alter symptoms at 4 h but counteracted ERP-P300 signs of diminished attention seen 2 weeks following placebo treatment. Secondary efficacy measures, including patient self-reports and parental ratings, found nicotine to reduce complex tics and improve behaviors related to inattention [104]. One study investigated neurophysiological mechanisms possibly underlying nicotine treatment of TS by using transcranial magnetic stimulation (TMS). A single dose of nicotine in 10 non-smoking and non-treated adults with TS reduced tic severity as assessed by blind video scoring in the majority of patients. In addition, nicotine abolished the reduced inhibition in patients compared to controls [172].

Tetrahydrocannabinol (THC) has been suggested to be effective and safe in the treatment of tics [162-164] without influence on neuropsychological performance [161]. This knowledge is based on a randomized, double-blind, placebo-controlled study in which 24 adult patients with TS were treated over a 6-week period with up to 10 mg THC/day. No serious adverse reaction occurred and the reported mild adverse reactions were dizziness, tiredness and dry mouth. Hasan et al. [98] reported about a 15-year-old boy with treatment refractory TS plus ADHD leading to severe physical and psychosocial impairment. For the first time after several years of unsuccessful medication even with a combination of different agents, the administration of THC improved tics considerably without adverse reactions, allowing parallel stimulant treatment of coexisting ADHD. Along with the THC treatment, TMS measured cortical inhibition was increased.

In addition to the use of pharmacological treatment options with systemic effects, there is increasing evidence for the efficacy of *botulinum toxin injections* to treat persistent well-localized (non-complex) motor and, sometimes, vocal tics by temporarily weakening the associated muscles. Initially, botulinum toxin injection was used for selected severe cases [3, 107, 125, 229]. Other case reports and case series followed also including children after the age of eight years [4, 131, 215, 257, 273, 279]. In 35 of 186 patients, botulinum toxin

injections were effectively controlling motor tics [8]. The effect on vocal tics was minimal. Adverse reactions included temporary soreness and mild muscle weakness. In 30 patients with vocal tics assessment after 15 days and then 4 times over a 12-month period botulinum toxin injection improved vocal tics in 93% of patients, with 50% being tic-free [187]. Mean response time was 5.8 days and mean duration of response was 102 days. Quality of life improved and premonitory experiences dropped from 53% to 20%. Hypophonia was the only adverse reaction of note (80% of patients). Just recently, the positive short-term and long-term (up to 10 years) treatment effects of botulinum toxin injections every 3 months on simple motor tics of 15 patients (mean age 43 years; range 18-84) could be shown [190]. Marras et al. [144] concluded from their randomized, double-blind controlled clinical trial that the treated tic frequency as well as the urge associated with the treated tic were reduced by botulinum toxin injection. Still, the patients' subjective perception was that overall this treatment did not improve their condition. This is perhaps due to the fact that only selected subset of tics could be treated in each patient.

The dopamine autoagonist *talipexole* with putative preferential activity on presynaptic dopamine receptors was investigated one time in a randomized, double-blind, placebo-controlled study [90]. In 13 adult men with TS talipexole was poorly tolerated because of clinically significant sedation and dizziness. Tics did not improve at tolerable doses. These findings suggest that talipexole has no role in the regular management of tic disorders.

Clonazepam, a benzodiazepine which acts primarily on the GABAergic system, has a long history in the treatment of TS with dosages up to 6 mg/day [89]. Although there have been no placebo-controlled trials in TS, open-label studies have been carried out in adults [94, 274] and adolescents with TS [115, 264]. In a single-blind comparison with clonidine in 20 children, clonazepam was superior in suppressing tics [61]. In a single-blind clinical study of 20 patients with TS, those with high red blood cell-to-plasma choline ratios responded better to clonazepam than to haloperidol [152]. As with all benzodiazepines, tolerance and adverse

reactions including sedation, short-term memory problems, ataxia, and paradoxical disinhibition often limit the use of clonazepam [89]. There are no data on other benzodiazepines except a case report about the therapeutic effect of low-dosage diazepam on facial tics in children [78].

The GABA B receptor agonist *baclofen*, which is used for the treatment of spasticity, has been examined in an open-label study in a large cohort of children with TS [8]. 250 of 264 patients on baclofen treatment experienced a significant decrease in the severity of tics. A small randomized, double-blind, placebo-controlled study of baclofen in 10 children was inconclusive because there was a reduction in overall impairment but no changes in tic frequency or severity [251]. The results of these studies provide only modest support for the use of baclofen in TS. Common adverse reactions were sedation and drowsiness.

Other GABAergic drugs including the anticonvulsant *levetiracetam* have shown tic reduction in open studies on TS [9, 71]. Adverse reactions, however, as well as the finding that levetiracetam did not change the mean total YGTSS and Clinical Global Impression score in a small randomized, double-blind crossover study (N=10) [99] as well as in a randomized, double-blind, placebo-controlled, crossover trial in 22 children with TS (mean age 12.2 years) [253] question its usefulness in the treatment of TS.

Topiramate reduced tics in a small randomized, double-blind study on 20 patients of a broad age range (7-65 years) compared to placebo [110]. This is in line with a chart review on 41 patients with TS [127] as well as a previous report on two patients with TS who were successfully treated with topiramate while previous medications were tapered and discontinued during the first 2 weeks of treatment [1].

Lithium has been used successfully to reduce tics in five of ten children and adolescents [121], a 22-year-old male [277], and three adolescents suffering from TS who had been initially treated with haloperidol [70]. Failure has also been described, though [26], and firmer evidence is lacking.

Several case reports [81, 220-222] and a randomized, double-blind, placebo-controlled study involving 10 adults with TS suggest that tic reduction may be achieved with *naloxone* [129], an opioid receptor antagonist. Some studies indicated that difference in response to naloxone in TS subjects may be based on a dose-response effect [38, 276].

Some attention has also been given to the use of treatments that include a modulation of the body's autoimmune-response. In children fulfilling criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS; a subgroup of children with OCD and/or tic disorder that experience symptom exacerbations following streptococcal infections), *plasma exchange* and *intravenous immunoglobulin (IVIG)* were both effective in lessening of symptoms [185, 293], although benefits through IVIG could not be confirmed in unselected patients with a tic disorder [101]. In a small prospective study, antibiotic prophylaxis with *penicillin* or *azithromycin* administered for 12 months in children fulfilling PANDAS criteria was associated with significant decreases in neuropsychiatric exacerbations [254]. A case study of a patient with TS reported benefits of treatment with *celecoxib*, a COX-2 inhibitor [165].

Finally, a *wide range of further neuroactive agents* have been examined non-systematically with divergent results concerning their efficacy in the treatment of TS. For example *bupirone* [65], *carbamazepine* [168, 292], *metoclopramide* [2, 169], *physostigmine* [258, 259], and *spiradoline mesylate* [39] have received some attention. A comprehensive overview of other case reports and non-blinded trials can be found elsewhere [195].

2.2.4 Treatment of tics in the context of comorbidities

Children and adolescents with TS are frequently affected by coexisting psychiatric conditions [79], which may be regarded the rule rather than the exception. In clinical samples of TS about half of the cases also meet criteria for ADHD and vice versa, TS is present in about 20% of children with ADHD [208, 228]. This co-occurrence of TS and ADHD is in

most cases associated with a higher psychopathological, social, and academic impairment resulting from the negative impact of ADHD [10, 95, 200-202]. Besides, patients with TS also suffer more frequently from obsessive-compulsive symptoms or disorder (about 50%). Especially the need to achieve a “just right” feeling in TS has to be seen as an indicator for a continuum between TS and OCD [203].

Coexisting disorders cause often more clinical impairment and may be more responsive to treatment than the tics themselves [19]. It is therefore crucial to select an appropriate treatment goal (tics or coexisting conditions), when deciding on treatment options. Treatment of tics and coexisting conditions should be prioritized according to the impairment caused by each problem (for a decision tree see figure1). Thus, in many cases not the tics, but coexisting problems require treatment e.g. ADHD or OCD. Clinicians should thus avoid to start two medications simultaneously, for instance one for tics and one for ADHD symptoms. Primary treatment of a coexisting condition, such as ADHD may reduce stress and improve attentional resources, and sometimes reduce tics by enhancing the individual's ability of tic suppression.

Treatment algorithms of coexisting conditions in the context of TS are similar to treatment of these conditions without the presence of TS. Well-designed controlled clinical trials have not indicated a deterioration of tics in persons treated with stimulants [21] nor induction of first tics by stimulant treatment even in children at risk [175, 204].

Long term treatment with methylphenidate (MPH) is neither associated with increases in tic severity. In a two year prospective, open label study in which effects of MPH treatment were evaluated in 34 prepubertal children with ADHD and with chronic multiple tic disorder, the authors found no evidence that motor or vocal tics changed in frequency or severity during the MPH maintenance therapy, whereas initial behavioral improvements were maintained [82]. In a subsequent blinded placebo-controlled discontinuation trial in 19 children with ADHD and with chronic tic disorder who had received psychostimulants for a minimum of

one year, tics did not change in their frequency or severity of motor or vocal tics during the maintenance dose of stimulant medication compared with the placebo condition. Treatment with the maintenance dose was, however, associated with behavioral improvement in ADHD symptoms, indicating continued efficacy. These studies prove that neither treatment nor discontinuation of treatment with MPH in patients with tics lead to an exacerbation of tics. Thus, abrupt withdrawal of stimulant medication in children receiving long-term maintenance therapy does not appear to result in worsening of tic frequency or severity.

Higher doses of stimulants, in the range of 45 mg b.i.d. of MPH and 22.5 mg b.i.d. of dexamphetamine, however, may still lead to (reversible) tic exacerbations [36]. Thus, in general, stimulants may be safely used in children with TS and ADHD, when using doses based on the typical clinical titration procedure [21]. Other treatment options for ADHD in the context of TS include clonidine [271], atomoxetine [5, 256], and desipramine [255].

Coexisting OCD in patients with TS may be less responsive to serotonin reuptake inhibitor monotherapy compared to OCD in patients without tics [149]. Co-administration of an antipsychotic agent may be helpful [20, 56].

3. Problems with clinical recommendations for the pharmacological treatment of TS

Unfortunately, there has not been great improvement in evidence concerning the pharmacological treatment of TS since the overview of Robertson and Stern [199] who stated that “the treatment of the Gilles de la Tourette syndrome has evolved from case reports, clinical experience and more recently blinded trials usually in small numbers of patients“. Ideally, according to the principles of evidence-based medicine to be recommended, an agent must have shown its efficacy in randomized, double-blind, placebo-controlled studies. However, even today, evidence for efficacy of many agents that might be considered in the pharmacological treatment of TS is often based on open studies or randomized, double-blind, placebo-controlled studies with quite small sample sizes [199]. Hence, there exists only one drug which has been approved for TS widely in Europe, which is haloperidol. However, because of its adverse reactions it is nowadays usually a drug of third line in clinical practice.

Particularly there is not a sufficient number of randomized, double-blind trials that have directly compared different pharmacological treatment options of TS including a placebo group (Ross and Moldofsky 1978; Shapiro, Shapiro et al. 1989; Sallee, Nesbitt et al. 1997). Moreover, the heterogeneity of tic disorders with regard to the severity, frequency, localization, complexity of the tics as well as with regard to patterns of comorbidity demands further investigation in terms of the identification of factors that may predict or moderate response to different psychopharmacological agents [199]. Knowledge in this area could help clinicians to reach a more tailored choice of treatments. Currently, we have no data with regard to response to a second medication in patients who did not respond favorably to a first line agent. That is, for example, in patients who have not responded to risperidone, we do not have scientific data from trials whether response may be still expected from another antipsychotic, or rather from a different type of medication. Finally, durations of existing studies have not always taken into account the natural waxing and waning of tics (see figure2). This calls for longer observation periods and better rating instruments than those of

most existing studies. Investigations of long-term efficacy and adverse reactions are completely lacking. Nevertheless, the treating physician should be aware of the side effects profile of the drug in question and initiate adequate and suitable clinical and laboratory controls.

Moreover, studies comparing the effectiveness of behavioral and pharmacological treatments in patients with TS are absent. Thus, currently no scientific data are available indicating whether behavioral treatment or medication should generally be tried first. An advantage of behavioral treatments may be its better long term effects, beyond the duration of the therapy, as well as their assumed less frequent and less severe adverse reactions. However, behavioral treatments require sufficient motivation and certain ability for introspection, which may limit its usefulness somewhat in younger patients (see also Verdellen et al., this issue). Patients' treatment preference after thorough psychoeducation is an important aspect in deciding between medication and behavioral therapy. Definitely, pharmacologic treatment should be initiated if behavioral treatment reveals insufficient success. Conversely, drug-treated patients who do not experience sufficient tic reduction and/or suffer from non-tolerable adverse reactions may be stimulated to (re-)start behavioral interventions. In the rare cases of adults, who have extremely impairing tics that are not sufficiently alleviated through several pharmacological treatment options one should consider deep brain stimulation (see Mueller-Vahl et al., this issue).

+++ figure1,2 and table1 about here +++

3.1 Assessing response to treatment

The clinician should inform the patient and their parents that the goal of a pharmacological treatment of TS is not to completely eliminate the tics, but to achieve a reduction aimed at eliminating the psychosocial impairment caused by the tics. Unrealistic

expectations on the efficacy of pharmacological treatment of TS will lead to frustration for the child, family, and physician. Also, the desire to completely suppress tics can lead to overmedication and adverse reactions that cause more problems than the tics themselves. A common example of this is the overtreatment of children to the point of excessive daytime sedation or unhealthy weight gain. Families should be informed that medication typically only results in a 25% to 50% reduction in tic symptoms.

Also, clinicians should always be aware of the natural waxing and waning of tics in TS when evaluating effects of treatments (see figure2). It is advisable to consistently use formal tic severity rating scales to more objectively assess responses to treatment over time. Perhaps the most suitable instrument is the YGTSS, a semi-structured interview which records the number, frequency, intensity, complexity, and interference of motor and vocal tics separately [135]. But also the Tourette Syndrome Severity Scale (TSSS) developed by Shapiro et al. [235], which is shorter and more easy to use can be recommended.

3.2 What specific agents can be recommended?

As previously stated, there is a great scarcity of studies directly comparing efficacy and safety of different psychopharmacological agents, foremost with regard to longer term effects. Therefore every general recommendation depends heavily on the experts' own experiences and preferences.

After reviewing the existing literature, it appears that the best evidence arising from randomized, double-blind, placebo-controlled studies is still available for the typical antipsychotics haloperidol and pimozide, with some indications that pimozide may be more effective and may have a somewhat more favorable adverse reaction profile than haloperidol [189], with exception of its potential cardiac effect. In clinical practice in Europe, however, over the last years haloperidol and pimozide have been replaced stepwise by atypical antipsychotics. Here, the best evidence is undoubtedly available for risperidone [186, 189].

However, this is also the agent that has been studied best. A lower risk for adverse reactions compared to typical psychotics is assumed in clinical use. Still many adverse reactions, however, are similar to those associated with the use of typical antipsychotics, including sedation, akathisia, weight gain, extrapyramidal symptoms (EPS), neuromalignant syndrome, and tardive dyskinesia. Although atypical antipsychotics generally are associated with a lower incidence of EPS in youth [269], a rapid dose escalation is actually associated with higher risk of EPS [37]. In addition, longer experience with atypical antipsychotics reveals that new risks need to be considered, such as metabolic syndromes and QTc prolongation. The incidence of these risks in patients suffering from TS, especially in children and adolescents, cannot be easily predicted due to the paucity of long-term studies in this population.

The choice of pharmacological treatments is not only based on the efficacy and the rate of adverse reactions but also on the potential to show efficacy in refractory cases. In particular, aripiprazole is rather promising, given the lower probability of weight gain as adverse reaction and promising effects in patients who had not responded to previous treatments. Placebo-controlled studies with aripiprazole are still missing, however.

Availability of clinical experience with agents also plays an important role in the choice of recommendable treatments. In the German-speaking world the benzamides, such as tiapride and sulpiride are commonly used as first line agents to treat TS particularly in children and adolescents. Indeed, tiapride is regarded as the medication of first choice in the German guidelines for the treatment of tic disorders without coexisting significant emotional/obsessive-compulsive symptoms [207], Tiapride and sulpiride are not available in the United States. This explains why these agents are not mentioned in reviews from US authors [87] and why their clinical efficacy in TS as well as their pharmacological properties have been underinvestigated in comparison to other antipsychotic compounds. This small base of evidence notwithstanding, Robertson and Stern [199] conclude in their review that

tiapride and sulpiride are highly recommendable to treat TS in view of their excellent balance of efficacy and tolerability proven over decades in clinical practice.

Further, severity of tics and presence of comorbidity may affect choices of treatments. Although the evidence in favor of the tic suppressing effects of clonidine may be less robust compared to the antipsychotics, clonidine may actually improve ADHD symptoms alongside with suppression of especially mild-to-moderate tics. In addition, clonidine tends to alleviate initial insomnia and reduce anxiety [217].

An important consideration, given the relative lack of controlled clinical studies, is the opinion of experts. Therefore, we sent by email a questionnaire to members of the European Society for the Study of TS (ESSTS). All clinicians with ample experience in the treatment of TS were asked what psychopharmacological agent they would consider first, second, third, and subsequent choices in the treatment of tics (provided there would be no contra-indication for any of the available agents, and there would be no comorbidity). We received 22 responses out of the 60 members. We rated each first choice agent with 4 points, a second choice agent with 3 points, a third-choice agent with 2 points, and additional agents with 1 point. As listed in table 1, most support from the experts has been provided for risperidone, with considerable support for clonidine, aripiprazole, and pimozide as well.

Based on the available evidence, experience with the drug, and experts' preference, risperidone can be recommended as a first choice agent for the treatment of tics. Adverse reactions form the biggest limitation of risperidone, foremost so weight gain and sedation. Other drugs merit recommendation as well. Relatively good evidence with a better adverse reaction profile than haloperidol is available for pimozide. Tiapride and sulpiride can be recommended based on the broad clinical experience and favorable adverse reaction profile, although more controlled clinical studies are required. Aripiprazole has great potential especially in treatment refractory cases and probably less pronounced risk of severe weight gain. Finally, clonidine can be given especially when coexisting ADHD is present. All other

agents mentioned in table 1 may be considered as alternatives, once response to one or more of the earlier mentioned medications has been unsatisfactory.

In case of coexisting OCD, risperidone forms a good first choice also, based on the results of clinical trials. This may be combined with a serotonin reuptake inhibitor. Given the continuum of tics and obsessive-compulsive symptoms, other agents recommended for the treatment of tics may be tried as well; when partial response occurs, addition of a serotonin reuptake inhibitor or of behavioral treatment may be considered. Coexisting ADHD may be treated with stimulants, atomoxetine, or clonidine. This may be combined with an (antipsychotic) agent for the tics.

The current guidelines do not contain dosage recommendations of each agent. In general, dosage should start low and gradually increase with close monitoring of response and adverse reactions. Most published studies have included both children and adults, up to date, no evidence suggests that the two age-groups should be treated in different ways apart from drug dosages [73, 199]. There are several hints that dosage of pharmacotherapy of TS is not different between children, adolescents, and adults once body weight has been taken into account [213, 282], but clear data are lacking. A commonly unrecognized problem is the miss of adapting the dosage to the increasing body weight during maturation.

To the best of our knowledge only one drug is formally licensed for the indication tics or TS in most European countries: haloperidol. With all other medications (actual exceptions of a certain country cannot be excluded), prescription is on an off-label base, reflecting the paucity of efficacy and safety data, which would not be sufficient for approval by a registration authority for any of the mentioned agents. This should always be discussed with families prior to initiation of treatment.

The proposed principles of practice are considered as guidelines only. We hope that this guideline may contribute to an improvement in the pharmacological management of patients with tic disorders. The individual treatment of a patient should be planned by

considering the available diagnostic information, the level of impairment associated with tics, the efficacy data and adverse reactions of treatment options as well as patient's preference to gain the best result and adherence possible.

Conflict of interest

Commercial firms and governmental organisations did not play a role in, or fund, the development of these guidelines. Kerstin J. Plessen, Renata Rizzo, Liselotte Skov, Gerd Strand, Jeremy Stern, Cristiano Termine, Pieter J. Hoekstra declare that they have no conflict of interest.

Veit Roessner: he has received lecture fees from Eli Lilly, Janssen-Cilag, Medice, Novartis, he was member of advisory boards of Eli Lilly, Novartis; Aribert Rothenberger (last three years): Advisory Board and Speakers Bureau of Lilly, Shire, Medice, Novartis, Research Support from Shire, German Research Society, Schwaabe, Travel Support from Shire, Educational Grant from Shire, Consultant of UCB/Shire, Lilly; Andrea Ludolph (last three years): she has received lecture fees from Janssen Cilag, and research funding from Novartis, she was/is involved in clinical trials with Böhringer Ingelheim, Eli Lilly, Janssen-Cilag;

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Table 1: Most common and important medication for pharmacologic treatment of Tourette Syndrome and other chronic tic disorders

Medication	Indication	Start Dosage (mg)	Therapeutic Range (mg)	Frequent Adverse Reactions	Physical Examinations– at Start and at Control	Level of Evidence
<i>Alpha-adrenergic Agonists</i>						
Clonidine	ADHD/TS	0.05	0.1-0.3	orthostatic hypotension, sedation, sleepiness	bloodpressure, ECG	A
Guanfacin	ADHD/TS	0.5-1.0	1.0-4.0	orthostatic hypotension, sedation, sleepiness	bloodpressure, ECG	A
<i>Typical Neuroleptics</i>						
Haloperidol	TS	0.25-0.5	0.25-15.0	EPS, sedation, increased appetite	bloodcount, ECG, weight, transaminases, neurologic status, prolactine	A
Pimozide	TS	0.5-1.0	1.0-6.0	EPS, sedation, increased appetite	bloodcount, ECG, weight, transaminases, neurologic status, prolactine	A
<i>Atypical Neuroleptics</i>						
Aripirazole	TS	2,50	2.5-30	sedation, akathisia, EPS, headache, increased appetite (less than other neuroleptics), orthostatic hypotension	bloodcount, bloodpressure, weight, ECG, transaminases, bloodsugar	C
Olanzapine	TS/OCB	2.5-5.0	2.5-20.0	sedation, increased appetite, akathisia	bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	B
Quetapine	TS	100-150	100-600	sedation, increased appetite, agitation, orthostatic hypotension	bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	C
Risperidone	TS/DBD	0.25	0.25-6.0	EPS, sedation, increased appetite, orthostatic hypotension	bloodcount, bloodpressure, ECG, weight, electrolytes, transaminases, prolactine, bloodlipids-and sugar	A
Ziprasidone	TS	5.0-10.0	5.0-10.0	EPS, sedation	Bloodcount, ECG, weight, transaminases, prolactine	A
<i>Benzamides</i>						
Sulpiride	TS/OCB	50-100 (2mg/kg)	2-10 mg/kg	problems with sleep, agitation, increased appetite	bloodcount, ECG, weight, transaminases, prolactine, electrolytes	B

Tiapride	TS	50-100 (2mg/kg)	2-10 mg/kg	sedation, increased appetite	bloodcount,ECG,weight, transaminases,prolactine, electrolytes	B
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DBD (disruptive behaviour disorder), OCB (obsessive-compulsive behaviour), TS (Tourette Syndrome), EPS (extrapyramidal symptoms). Evidence level: A (>2 controlled randomized trials), B (1 controlled, randomized trial), C (case studies, open trials)

Table 2. European experts' recommendation for the treatment of tics for children and adolescents, based on response to the question, which medication the expert clinician would consider first, second, third, and subsequent choices in, provided there would be no contra-indication for any of the available agents and no comorbidity. ¹

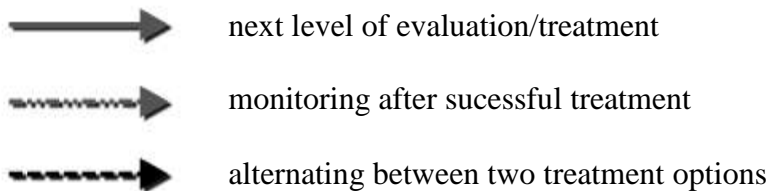
Agent	Expert rating
Risperidone	60
Clonidine	37
Aripiprazole	33
Pimozide	32
Sulpiride	24
Tiapride	21
Haloperidol	17
Tetrabenazine	9
Ziprasidone	6
Quetiapine	4
Tetrahydrocannabinol	2
Desipramine	1
Botulinum toxin	1
Thioridazine	1
Tetrahydrocannabinol	1
Guanfacine	1
Oxcarbazepine	1
Atomoxetine	1

¹We received 22 responses out of 60 questionnaires and rated each first choice agent with 4 points, a second choice agent with 3 points, a third-choice agent with 2 points, and additional agents with 1 point.

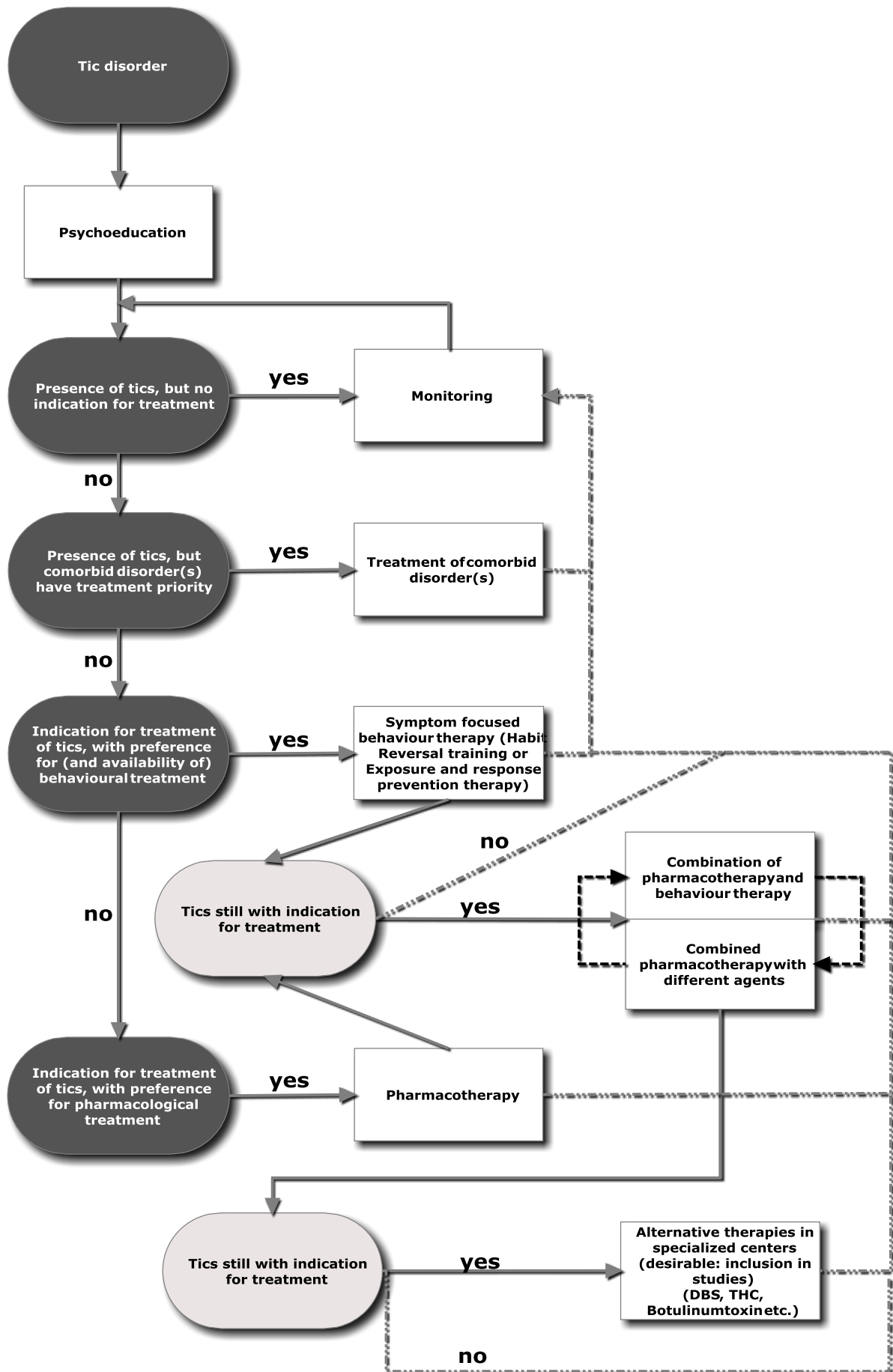
Figure 1: **Decision tree for the treatment of tic disorders including Tourette Syndrome.**

Indications for treatment (details are given in the manuscript):

- *Tics cause subjective discomfort (e.g. pain or injury).*
- *Tics cause sustained social problems for the patient (e.g. social isolation or bullying).*
- *Tics cause social and emotinal problems for the patient (e.g. reactive depressive symptoms)*
- *Tics cause functional interference (e.g. impairment of academic achievements)*



Note: patient preference (after psychoeducation) and availability of therapists have to be considered in the choice of treatment. DBS = deep brain stimulation, THC = Tetrahydrocannabinol.



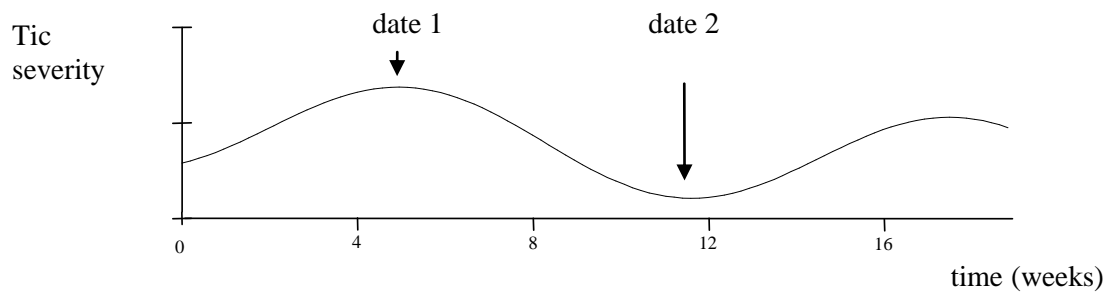


Figure 2: **Evaluation of treatment efficacy in TS in light of natural waxing and waning.**

At date 1 a therapeutic intervention could be followed by tic reduction despite of its potential to increase tics or without an effect on tics. This has to be ascribed not to causal mechanisms of the intervention but to the natural waxing and waning of the tics.

Correspondingly, a therapeutic intervention at date 2 could be followed by an increase of TS symptomatology despite its potential to reduce tics. The therapeutic intervention might attenuate the natural waxing of the tics.

Conclusion: Meaningful appraisal of treatment efficacy in TS can only be given in most cases after longer time.