OPINION ARTICLE

REVISED Is Tourette syndrome a rare condition? [version 2; peer review: 2 approved]

Previously titled, 'Is Tourette syndrome a rare disease?'

Andreas Hartmann[1], Natalia Szejko[2,3], Nanette Mol Debes[4], Andrea E. Cavanna[5-7], Kirsten Müller-Vahl[8]

[1]National Reference Center for Tourette Syndrome, Department of Neurology, Groupe Hospitalier Pitié-Salpêtrière, Paris, 75013, France
[2]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[3]Department of Bioethics, Medical University of Warsaw, Waraw, Poland
[4]Department of Pediatrics, Herlev University Hospital, Copenhagen, Denmark
[5]Department of Neuropsychiatry, BSMHFT and University of Birmingham, Birmingham, UK
[6]School of Life and Health Sciences, Aston University, Birmingham, UK
[7]Institute of Neurology, University College London, London, UK
[8]Clinic of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany

v2 **First published:** 02 Jun 2021, **10**:434
https://doi.org/10.12688/f1000research.53134.1
Latest published: 02 Nov 2021, **10**:434
https://doi.org/10.12688/f1000research.53134.2

Abstract

Based on its prevalence, Tourette syndrome cannot be considered a rare condition. However, in this opinion article, we make the claim that it should nonetheless be considered as an orphan or neglected disease.

Keywords

Tourette syndrome, tics, rare disease, orphan disease

This article is included in the Tics collection.

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 02 Nov 2021	✓ report	✓ report
version 1 02 Jun 2021	✓ report	? report

1. **Peter Nagy**, Vadaskert Hospital and Outpatient, Budapest, Hungary

2. **Tammy Hedderly**, Evelina Children's Hospital, London, UK
Osman Malik, Guy's and St Thomas's, London, UK
Tamsin Owen, Guys and St Thomas's NHS Trust, London, UK

Any reports and responses or comments on the

article can be found at the end of the article.

Corresponding author: Andreas Hartmann (andreas.hartmann@aphp.fr)

Author roles: Hartmann A: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Szejko N**: Writing – Original Draft Preparation, Writing – Review & Editing; **Mol Debes N**: Writing – Original Draft Preparation, Writing – Review & Editing; **Cavanna AE**: Writing – Original Draft Preparation, Writing – Review & Editing; **Müller-Vahl K**: Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: Andreas Hartmann has received consultant's honoraria from Lundbeck and Noema Pharma. Natalia Szejko: None. Nanette Mol Debes: None. Andrea E. Cavanna: None. Kirsten Müller-Vahl: Financial or material research support from EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978) DFG: GZ MU 1527/3-1 and GZ MU 1527/3-2, BMBF: 01KG1421, National Institute of Mental Health (NIMH), Tourette Gesellschaft Deutschland e.V. Else-Kröner-Fresenius-Stiftung, GW pharmaceuticals, Almirall Hermal GmbH, Abide Therapeutics, and Therapix Biosiences. She has received consultant's honoraria from Abide Therapeutics, Boehringer Ingelheim International GmbH, Bionorica Ethics GmbH, CannaMedical Pharma GmbH, Canopy Grouth, Columbia Care, CTC Communications Corp., Demecan, Eurox Deutschland GmbH, Global Praxis Group Limited, IMC Germany, Lundbeck, Sanity Group, Stadapharm GmbH, Synendos Therapeutics AG, and Tilray. She is an advisory/scientific board member for CannaMedical Pharma GmbH, Bionorica Ethics GmbH, CannaXan GmbH, Canopy Growth, Columbia Care, IMC Germany, Leafly Deutschland GmbH, Sanity Group, Syqe Medical Ltd., Therapix Biosciences Ltd., and Wayland Group. She has received speaker's fees from Aphria Deutschland GmbH, Almirall, Cogitando GmbH, Emalex, Eurox Deutschland GmbH, Ever pharma GmbH, Meinhardt Congress GmbH, PR Berater, Spectrum Therapeutics GmbH, Takeda GmbH, Tilray, Wayland Group. She has received royalties fromDeutsches Ärzteblatt, Der Neurologie und Psychiater, Elsevier, Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, and Kohlhammer. She served as a guest editor for Frontiers in Neurology on the research topic "The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects", is an associate editor for "Cannabis and Cannabinoid Research" and an Editorial Board Member of "Medical Cannabis and Cannabinoids" und "MDPI-Reports" and a Scientific board member for "Zeitschrift für Allgemeinmedizin".

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Hartmann A, Szejko N, Mol Debes N *et al.* **Is Tourette syndrome a rare condition? [version 2; peer review: 2 approved]** F1000Research 2021, **10**:434 https://doi.org/10.12688/f1000research.53134.2

First published: 02 Jun 2021, **10**:434 https://doi.org/10.12688/f1000research.53134.1

REVISED **Amendments from Version 1**

In the revised version of the manuscript, we have changed the title and used the word "condition" instead of "disease". We have also expanded on the need for further longitudinal research on the course of TS as highlighted by both reviewers. Finally, we have inserted a new paragraph regarding the question to what extent TS is part of the neurodiversity spectrum and when it is a condition requiring medical attention.

Any further responses from the reviewers can be found at the end of the article

What is a rare disease?

Rare diseases are diseases which affect a small number of people compared to the general population. In Europe, a disease is considered to be rare when it affects 1 person per 2,000.[1] In contrast, the European Commission on Public Health[2] defines rare diseases not only based on low prevalence (<1 in 2,000 people), but in addition as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them." Accordingly, diseases that are statistically rare, but not also life-threatening, chronically debilitating, or inadequately treated, are excluded from this definition. In the United States, the Rare Diseases Act of 2002[3] also defines rare disease strictly according to prevalence, but on the basis of different rates, as follows: "Any disease or condition that affects fewer than 200,000 people in the United States", or about 1 in 1,500 people.[4]

Because of definitions that include reference to treatment availability, a lack of resources, and severity of the disease, the term "orphan disease" has been introduced as a synonym for "rare disease". Interestingly, in the United States and the European Union, orphan diseases have a distinct legal meaning. Originally, the orphan drug movement began in the United States. The United States Orphan Drug Act[5] summarizes under the term "orphan diseases" both rare diseases and any non-rare diseases "for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug". Similarly, the European Organization for Rare Diseases (EURORDIS[6]) also includes both rare diseases and neglected diseases into a larger category of "orphan diseases".

Definition(s) of Tourette syndrome

Tourette syndrome (TS) is defined by the DSM-5 as a chronic tic disorder with the presence of at least two motor and one vocal tics over a period >12 months in someone under the age of 18 after excluding secondary causes (APA, 2013). This definition is not substantially different from that given by the previous version, the DSM-IV-TR, on which the current epidemiological literature is based. However, there was a major shift between the initial version of the DSM-IV and its revision: it was no longer a requirement that tics must be *debilitating*. This essentially descriptive vision of TS has its merits as it is difficult if not impossible to define operational criteria for what can be considered debilitating. Also, the waxing and waning nature of tics, both phenomenologically and with regard to severity, means that impairment may vary over time, even if the overall condition can be considered chronic. However, this very broad definition of TS also means that likely many people fall under this diagnostic umbrella category who do not at all require medical attention at any time during their life. The need to achieve a balance between the gains and losses resulting from the removal of the "impairment" criterion could be fruitfully reassessed a few decades after the change took place. The positive repercussions have been particularly manifest in the domain of research (e.g. inclusion of milder cases in genetic studies, cf. Müller-Vahl *et al.*, 2019). However, over time many clinicians working in specialist settings have noticed that a substantial degree of overlap between the definition of TS and what is observed in everyday clinical practice has inevitably been lost. In this respect, we acknowledge that there is an ongoing debate on whether to ground TS – among other neurodevelopmental conditions such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) – in the neurodiversity field. Which means, among other things, letting go of terms like "disease" or "disorder", at least for a subset of concerned people, as these may be considered stigmatizing. For the same reason we do not encourage the use of terms like "handicap" or "disability" in relation to these conditions. We consider this debate to be important, but we endorse the premise that people with tics typically seek medical attention out of their own volition (there is no need to advertise our services and waiting lists are, unfortunately, much too long – see below). Therefore, we posit that terms such as "disease" of "disorder" are not entirely out of place, even though we fully acknowledge that impairment related to tics and/or comorbidities can fluctuate significantly, both inter- and

[1]https://en.wikipedia.org/wiki/Rare_disease.
[2]https://en.wikipedia.org/wiki/European_Commission.
[3]https://en.wikipedia.org/wiki/Rare_Diseases_Act_of_2002.
[4]https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.
[5]https://en.wikipedia.org/wiki/Orphan_Drug_Act.
[6]www.eurordis.org.

intra-individually (see above). In consideration of such fleetingness, we are not in favour of reintroducing the 'impairment' criterion to the DSM – we simply point out that its removal has created problems of its own. However, in our opinion, there is no perfect solution to these dilemmas, just compromises. At the end of the day, classifications (DSM, ICD and others) and the way medical departments are structured are rather irrelevant when compared to the demands people in need – suffering people – place on us. Calling these people "patients" carries no stigma in our opinion: one wonders why any medical diagnosis should carry stigma, to begin with. Moreover, it can be argued that some bullying and harassment people with TS experience stems precisely from the fact that their tics are not recognized as a movement disorder; rather, they find themselves accused of "doing it on purpose", of trying to attract attention, etc. Therefore, a fine line is being thread.

Epidemiology of Tourette syndrome

Recent epidemiological studies of TS have estimated its prevalence between 0.3 to 0.7% in school-aged children (Knight *et al.*, 2012; Scharf *et al.*, 2015). A conservative estimate would be around 0.5%, that is one child in 200, 10 times the accepted rate for a rare disease. In adults there is no solid epidemiological data although we may extrapolate for the pediatric findings. Assuming that two thirds of patients with TS remit when entering adulthood (Leckman *et al.*, 1998), around 0.2% of adults might still suffer from TS, which still does not fulfill any of the diagnostic criteria for rare diseases given above. A recent meta-analysis based on only three studies, however, suggested a prevalence rate of 0.012%, which would make adult TS indeed a rare disease (Levine *et al.*, 2019). Clearly, more epidemiological research is warranted in the field of adult TS.

The problem

What experts on TS agree on is that the condition is underdiagnosed, and the delay between onset of symptoms (tics) and diagnosis is too long (Mol Debes *et al.*, 2008; Shilon *et al.*, 2008). Yet, they also acknowledge that a substantial number of people, regardless of age (but likely more adults) remain unbothered by their tics and live perfectly normal lives; in other words, they never seek medical attention and have no reason to do so. Based on this fact, the term "tic spectrum disorder" has been suggested including all variants and severity levels of the disease (Müller-Vahl *et al.*, 2019).

However, in an ideal world, how many people with TS according to DSM-5 criteria might legitimately be called *patients*? We speculate the percentage to be around 10-20%. One of the strategies to tackle this problem could be division of patients with TS in clinical subgroups mainly dependent on tic severity. According to this premise, severe TS is indeed, and thankfully, a rare condition. But here also, tolerance to tics and their sequalae, both social and functional, differ enormously from patient to patient, so defining operational criteria or some sort of cut-off (i.e., on the Yale Global Tic Severity Scale) will most likely be impossible. A further strategy could be pursued by focusing on the complexity or phenotype – with and without comorbidity – of the clinical picture of TS. This strategy might involve a return to the origin, namely to Gilles de la Tourette's original definition of TS, which encompasses the symptom triad of tics, echolalia, and coprolalia. The condition presenting with both simple and complex tics is sometimes referred to as "full-blown TS" and would arguably qualify for the "rare disease" category (Cavanna, 2018). The abovementioned strategies would lead to the identification of a subgroup of patients whose condition bears a clinically relevant impact on quality of life. This pathway could compensate for the information lost with the removal of the "impairment" criterion from the revised set of diagnostic criteria for TS in the DSM-IV-TR (2000). Of note, there have also been efforts to define evidence-based TS subgroups through factor or cluster analyses, although these have not yet had a significant impact on diagnosis and management (cf. Cravedi et al., 2018). Finally, and in this respect, one of the most important tasks in TS research will be to gather more solid epidemiological and longitudinal data (Black et al., 2021).

A proposal

Although tics are a common symptom, we wish to officially continue considering TS a rare (or orphan) disease because of certain public health (and other) benefits this implies. Clearly, TS is underrecognized (or misrepresented – Fat *et al.*, 2012) and underdiagnosed, so, *de facto*, rare for treating physicians and other health care professionals. There is very little targeted drug research for the treatment of tics to date, and in most patients off-label prescriptions are made. For these reasons, we might reasonably call TS a *neglected* disease, needing further support as a "rare disease" by policy makers until things change. In other words, TS as such might not be rare per se, but there clearly is a paucity of available and accessible treatments for this patient population. Those insisting on high prevalence of TS to increase support/awareness of this condition may, ironically, render a disservice to patients. Similar to patients with essential tremor, we will then be left to our own devices in the no man's land between public and industrial support, and progress may slowly grind to a halt.

Data availability

No data is associated with this article.

References

American Psychiatric Association: **DSM-5 Diagnostic Classification**. In: *Diagnostic and Statistical Manual of Mental Disorders.* 2015.

Black KJ, Kim S, Yang NY, *et al.*: **Course of tic disorders over the lifespan.** *Curr Dev Disord Rep.* 2021 Jun; **8**(2): 121–132. Epub 2021 Apr 10.
PubMed Abstract | Publisher Full Text

Cavanna AE: **The neuropsychiatry of Gilles de la Tourette syndrome: The état de l'art.** *Rev Neurol (Paris).* 2018 Nov; **174**(9): 621–627.
PubMed Abstract | Publisher Full Text

Cravedi E, Deniau E, Giannitelli M, *et al.*: **Disentangling Tourette syndrome heterogeneity through hierarchical ascendant clustering.** *Dev Med Child Neurol.* 2018 Sep; **60**(9): 942–950. Epub 2018 May 10.
PubMed Abstract | Publisher Full Text

Fat MJ, Sell E, Barrowman N, *et al.*: **Public perception of Tourette syndrome on YouTube.** *J Child Neurol.* 2012 Aug; **27**(8): 1011–1016.
PubMed Abstract | Publisher Full Text

Knight T, Steeves T, Day L, *et al.*: **Prevalence of tic disorders: a systematic review and meta-analysis.** *Pediatr Neurol.* 2012 Aug; **47**(2): 77–90.
PubMed Abstract | Publisher Full Text

Leckman JF, Zhang H, Vitale A, *et al.*: **Course of tic severity in Tourette syndrome: the first two decades.** *Pediatrics.* 1998 Jul; **102**(1 Pt 1): 14–19.
PubMed Abstract | Publisher Full Text

Levine JLS, Szejko N, Bloch MH: **Meta-analysis: Adulthood prevalence of Tourette syndrome.** *Prog Neuropsychopharmacol Biol Psychiatry.* 2019 Dec 20; **95**: 109675.
PubMed Abstract | Publisher Full Text

Mol Debes NM, Hjalgrim H, Skov L: **Limited knowledge of Tourette syndrome causes delay in diagnosis.** *Neuropediatrics.* 2008 Apr; **39**(2): 101–105.
PubMed Abstract | Publisher Full Text

Müller-Vahl KR, Sambrani T, Jakubovski E: **Tic disorders revisited: introduction of the term "tic spectrum disorders".** *Eur Child Adolesc Psychiatry.* 2019 Aug; **28**(8): 1129–1135. Epub 2019 Jan 19.
PubMed Abstract | Publisher Full Text | Free Full Text

Scharf JM, Miller LL, Gauvin CA, *et al.*: **Population prevalence of Tourette syndrome: a systematic review and meta- analysis.** *Mov Disord.* 2015 Feb; **30**(2): 221–228. Epub 2014 Dec 8.
PubMed Abstract | Publisher Full Text

Shilon Y, Pollak Y, Benarroch F, *et al.*: **Factors influencing diagnosis delay in children with Tourette syndrome.** *Eur J Paediatr Neurol.* 2008 Sep; **12**(5): 398–400. Epub 2007 Dec 4.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 03 November 2021

https://doi.org/10.5256/f1000research.78188.r98694

✔ **Peter Nagy**
Vadaskert Hospital and Outpatient, Budapest, Hungary

Thank for the responses, I have no further comment.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neurodevelopmental disorders, psychopharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 03 November 2021

https://doi.org/10.5256/f1000research.78188.r98693

✔ **Tammy Hedderly**
Tic and Neurodevelopmental Movements Service (TANDeM), Evelina Children's Hospital, London, UK
Osman Malik
Evelina London Children's Healthcare, Guy's and St Thomas's, London, UK
Tamsin Owen
TANDeM, Evelina London Children's Healthcare, Guys and St Thomas's NHS Trust, London, UK

Thank you to the authors for providing a clearer explanation to the proposals and for also highlighting important points for future debate in our field. We are happy to agree to the

submissions and look forward to further discussions as always. TH

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Paediatric Movement Disorders and Neurodevelopmental medicine

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 16 July 2021

https://doi.org/10.5256/f1000research.56487.r87458

?

Tammy Hedderly
Tic and Neurodevelopmental Movements Service (TANDeM), Evelina Children's Hospital, London, UK
Tamsin Owen
TANDeM, Evelina London Children's Healthcare, Guys and St Thomas's NHS Trust, London, UK
Osman Malik
Evelina London Children's Healthcare, Guy's and St Thomas's, London, UK

This viewpoint article, with its interesting challenge to consider Tourette syndrome (TS) as a rare (or orphan) disease, has come during an unfortunate moment in time where we are experiencing a Covid associated pandemic of tic and tic-like-movements referrals (Heyman, Liang and Hedderly 2021). We are reflecting on these concepts whilst also sitting amongst an ever-increasing pile of new referrals for children and adolescents with a dramatic increase in tics and functional tic-like attacks, making the current prevalence rate far from 'rare'.

The viewpoint paper opens with a title that, in itself, raises controversy. Should TS even be considered a disease at all? When engaging with some of the children and families with tics we often embrace terms such as developmental differences and neuro diversity so as to reduce the stigma sometimes associated with tics. We often encourage children to re-frame their tics and co-morbidities as diversity and difference in order to focus on some of the benefits this neurodiversity brings (for example heightened attention to detail, perfectionist traits or special abilities to switch attention)We routinely do this when the situation allows accepting, of course, for some of the 'patients' that more detailed therapeutic strategies are needed to enable individuals to achieve a therapeutic goal. Should the term disease be therefore removed from the discussion?

The proposed postulate should probably remind us all of the lively (and fun) debate held at the

European Society of Tourette Syndrome (ESSTS) in Copenhagen in 2018 (?) when we were all fortunate enough to meet face to face. At this meeting, we asked if 'Syndrome' within Tourette should be replaced with 'spectrum' instead, a discussion which helpfully involved those with lived experience of Tourette syndrome. To our unit's surprise the vote was in favour of keeping the term syndrome, as we had personally changed to using the term Tic/Tourette Spectrum within our own clinical service in 2012. We published our rationale for this in a paediatric journal (Malik and Hedderly 2018) and our unit's patient surveys revealed a preference for this term. We were pleased to see that our colleagues in Germany (Muller-Vahl 2019) support this preference. We feel this user-led preference for less pathologizing language supports not viewing Tourette syndrome as a disease. It would be interesting to hear the views of individuals with lived experience of Tourette syndrome about the palatability of the term "rare disease" to describe their symptoms.

This viewpoint paper provides an engaging discussion around how definitions of rarity of disease and orphan status vary depending on which area the reader sits in, whether in UK, USA or in the European Commission of Public Health. An informative point is raised about the lack of operational criteria for applying the term 'debilitating' and the removal if this criteria in DSM -V. The authors also point out helpfully that when using the term 'wax and wane' the clinicians should remember this does not just apply to the tic phenomenology but also to how impairing the symptoms are at any given time, although personally we recommend avoiding the use of the term handicap. This is so that we can fully respect people presenting with difficulties or with disability as individuals who can still have control over their own lives.

In this article, the term TS is highlighted to be used very much as an umbrella term including people with no presenting complaints and those who do not seek medical attention. The authors appear to advocate a re-evaluation of the term 'impairment' from the diagnostic criteria, whilst at the same time acknowledging that removing this term has had some positive benefits such as allowing for more cases to be included in genetic studies.

The final position is not entirely clear and we would like to propose the need to consider the views of a user group-the children, adolescents and adults experiencing tics and symptoms or signs of Tourette Spectrum conditions. We would propose again the need to identify different clusters and subgroups of 'Tourette experiencers' and, although tics will be at the core of each cluster, we would propose that the defining features of different groups should not involve markers of tic severity at all moving away from the importance placed on using the 'tic count'.

The presence of the co-occuring conditions with a detailed formulation around driving forces to the tics are probably much more relevant (i.e. cluster groups). For example, in the novel currently exploding phenotype which (in our UK experience) has a higher representation of teenage girls with marked social anxiety and self-harm rates reaching 44%, we also see other groups with toe walking and autism traits and the emotionally dysregulated inattentive boys. The clinical cluster view involves making a patient-led, hierarchy of important 'wishes' to prioritise for potential modification.

We propose that the social and functional difficulties described following tics may be better viewed as primary drivers of tics in some families and not just sequalae, as mentioned in the viewpoint paper. We understand that potentially histaminergic, serotoninergic, dopaminergic, glutaminergic genes and pathways are involved in the generation of tics and tic-like behaviour and in the co-occuring mental health associations. The decision about how rare or not a Tic cluster

may be will probably depend on the old dilemma of 'lumping vs splitting'. Some of the newer bioinformatic approaches of research will ultimately answer the question of which of the pathogenetic mechanisms underpinning the Tourette Spectrum are rarer that the others.

In conclusion, we would propose that Tourette syndrome should not be considered a rare disease due to the current prevalence rates, the potential impact on the user group and a need to consider the often frequent co-occurring symptoms. We prioritise an approach which includes the provision of a strength- and needs-based formulation. It is of course imperative to hold user-led consultations regarding these discussions. In the meantime, we would propose not calling TS rare or an orphan 'disorder or disease' and instead highlight that a major problem in the field is the 'rarity' of available and accessible treatments. In the UK the CAMHS services are overloaded and our movement disorder clinics have long waiting lists to even get to the point of diagnosis. Therapists trained in the management of tics or functional tic like episodes are scarce. Working together we must aim to address the orphan-ness or rarity of the resources to help provide solutions to the users with ever-increasing problems that we are all seeing in our clinics.

References:

Malik O, Hedderly T. Childhood tic disorders: diagnosis and management. Symposium: Neurology| Volume 28, Issue 10, P445-453, October 01, 2018

Müller-Vahl KR, Sambrani T, Jakubovski E. Tic disorders revisited: introduction of the term "tic spectrum disorders". Eur Child Adolesc Psychiatry. 2019 Aug;28(8):1129-1135.

Heyman I, Liang H, Hedderly T. COVID-19 related increase in childhood tics and tic-like attacks. Arch Dis Child. 2021 Mar 6:archdischild-2021-321748. doi: 10.1136/archdischild-2021-321748. Epub ahead of print. PMID: 33677431.

References

1. Heyman I, Liang H, Hedderly T: COVID-19 related increase in childhood tics and tic-like attacks. *Arch Dis Child*. 2021. PubMed Abstract | Publisher Full Text
2. Malik O, Hedderly T: Childhood tic disorders: diagnosis and management. *Paediatrics and Child Health*. 2018; **28** (10): 445-453 Publisher Full Text
3. Müller-Vahl KR, Sambrani T, Jakubovski E: Tic disorders revisited: introduction of the term "tic spectrum disorders".*Eur Child Adolesc Psychiatry*. 2019; **28** (8): 1129-1135 PubMed Abstract | Publisher Full Text

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Paediatric Movement Disorders and Neurodevelopmental medicine

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 26 Jul 2021

Andreas Hartmann, Groupe Hospitalier Pitié-Salpétriére, Paris, France

We thank Dr Hedderly for her thoughtful comments.

To begin with, we acknowledge that there is an ongoing debate on whether to ground TS – among other neurodevelopmental conditions such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) – in the neurodiversity field. Which means, among other things, letting go of terms like “disease” or “disorder”, at least for a subset of concerned people, as these may be considered stigmatizing. And, as also mentioned by Dr Hedderly, refrain for using terms like “handicap” or “disability” in relation to these conditions. We consider this debate to be important, but it is not specifically the subject of our article as we depart from three premises: (i) that TS is listed in the DSM-5 and thus, by definition, a medical condition; and (ii) that various health care professionals are following people with tics; and (iii) most importantly – that people with tics seek medical attention out of their own volition (there is no need to advertise our services and waiting lists are, unfortunately, much too long, see below). Therefore, we posit that terms such as “disease” of “disorder” are not entirely out of place, even though we fully acknowledge that impairment related to tics and/or comorbidities can fluctuate significantly, both inter- and intra-individually, as also stated in our article. Because of that fleetingness, we are actually not in favour of reintroducing the ‘impairment’ criterion to the DSM – we simply point out that removing it has created problems of its own. However, in our opinion, there is no perfect solution to these dilemmas, just compromises. At the end of the day, classifications (DSM, ICD and others) and the way medical departments are constructed are rather irrelevant when compared to the demands people in need – *suffering* people – place on us. And, calling these people “patients” carries no stigma in our opinion: one wonders why any medical diagnosis should carry stigma, to begin with. Moreover, it can be argued that some bullying and harassment people with TS experience stems precisely from the fact that their tics are not recognized as a movement disorder; rather, they find themselves accused of “doing it on purpose”, of trying to attract attention, etc.

As we may agree that some people may be incapacitated from tics and comorbidities, Dr Hedderly indeed points out that our departments are in high demand, with severe case loads and long waiting lists. And this is where our points of view merge: neither chronic tics nor TS are rare, numerically speaking (again, we simply conform to official definitions of rarity – 1:2000 prevalence rate – which can be debated in itself); but there are not enough trained experts, providers, and infrastructure around to adequately take care of these

patients. Which, in effect, makes TS rare which is, for us, a matter-of-fact statement – but also a call for action. This unsatisfactory situation may be an opportunity to secure support and funding from regional, national or European bodies to help the TS community – both patients and healthcare providers. One example is COST action BM905 (2010-2014) which was instrumental in creating a European network on TS and gave a tremendous boost to the European Society for the Study of Tourette Syndrome (ESSTS); which, since its inception, has always entertained close ties to patient associations which have now organized in an international network (Tics and Tourette across the Globe - TTAG).

So, to rephrase: TS is not rare but should be supported as such by public bodies as long as adequate research and medical care is not available in so many countries around the globe. Once TS has become more "mainstream" and is on the map of the general public, government agencies, but also the private sector, and across countries and continents, we'll be happy to join the ranks of non-rare (common) diseases.

Competing Interests: No competing interests were disclosed.

Author Response 04 Oct 2021

Andreas Hartmann, Groupe Hospitalier Pitié-Salpétriére, Paris, France

We thank Dr Hedderly for her thoughtful comments.

To begin with, we acknowledge that there is an ongoing debate on whether to ground TS – among other neurodevelopmental conditions such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) – in the neurodiversity field. Which means, among other things, letting go of terms like "disease" or "disorder", at least for a subset of concerned people, as these may be considered stigmatizing. For the same reason, as also mentioned by Dr Hedderly, we refrain from using terms like "handicap" or "disability" in relation to these conditions. We consider this debate to be important, but it is not specifically the subject of our article as we endorse three premises: (i) that TS is listed in the DSM-5 and thus, by definition, a medical condition; (ii) that various health care professionals are involved in the care of people with tics; and (iii) most importantly – that people with tics typically seek medical attention out of their own volition (there is no need to advertise our services and waiting lists are, unfortunately, much too long - see below). Therefore, we posit that terms such as "disease" of "disorder" are not entirely out of place, even though we fully acknowledge that impairment related to tics and/or comorbidities can fluctuate significantly, both inter- and intra-individually, as also stated in our article. In consideration of such fleetingness, we are actually not in favour of reintroducing the 'impairment' criterion to the DSM – we simply point out that its removal has created problems of its own. However, in our opinion, there is no perfect solution to these dilemmas, just compromises. At the end of the day, classifications (DSM, ICD and others) and the way medical departments are structured are rather irrelevant when compared to the demands people in need – *suffering* people – place on us. Calling these people "patients" carries no stigma in our opinion: one wonders why any medical diagnosis should carry stigma, to begin with. Moreover, it can be argued that some bullying and harassment people with TS experience stems precisely from the fact that their tics are not recognized as a movement disorder;

rather, they find themselves accused of “doing it on purpose”, of trying to attract attention, etc. We have incorporated these points in the revised version of the manuscript. We have also changed the title by using “condition” instead of “disease”, even though this term cannot be avoided entirely when speaking of research initiatives and networks in this domain. Finally, we would like to remind of the question mark in the title and the ”proposal” in the end: this is an opinion paper supposed to stimulate discussion on an admittedly complicated topic, not scripture.

As we agree that some people may be incapacitated by their tics and comorbidities, Dr Hedderly indeed points out that our departments are in high demand, with severe caseloads and long waiting lists. And this is where our points of view merge: neither chronic tics nor TS are rare, numerically speaking (again, we simply conform to official definitions of rarity – 1:2000 prevalence rate – which can be debated in itself); but there are not enough trained experts, providers, and infrastructure around to adequately take care of these patients. This, in practical terms, makes TS rare which is, for us, a matter-of-fact statement – but also a call for action. This unsatisfactory situation may be an opportunity to secure support and funding from regional, national, or European bodies to help the TS community – both patients and healthcare providers. One example is COST action BM905 (2010-2014) which was instrumental in creating a European network on TS and gave a tremendous boost to the European Society for the Study of Tourette Syndrome (ESSTS). Since its inception, ESSTS has consistently entertained close ties to patient associations which have now organized in an international network (Tics and Tourette across the Globe - TTAG).

As to the recent surge in functional tics, these are not the subject of our article, and we do not consider them to be a variant of TS but rather a separate entity (Müller-Vahl et al., 2021). However, we agree that these patients put an additional strain on our already overstretched capacities.

Concerning definition of evidence-based clusters, this point has also been raised by Dr Nagy, and modifications were made to the manuscript. We agree that this is an important endeavour and, of course, these clusters precisely incorporate comorbidities and move beyond what Dr Hedderly refers to as the ‘tic count’. As TS professionals, we have neither felt nor stated that tics are the sole source of impairment. Likewise, instead of arguing that tics drive social and functional difficulties, we have acknowledged a bidirectional relationship.

So, to rephrase: TS is not rare but should be supported as such by public bodies, as long as adequate research and medical care is not available in so many countries around the globe. Once TS has become more “mainstream” and features more prominently in the radar of the general public, government agencies, but also the private sector, and across countries and continents, we’ll be prepared to join the ranks of non-rare (common) conditions.

Müller-Vahl KR, Pisarenko A, Jakubovski E, Fremer C. Stop that! It's not Tourette's but a new type of mass sociogenic illness. Brain. 2021 Aug 23:awab316. doi: 10.1093/brain/awab316. Epub ahead of print. PMID: 34424292.

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 June 2021

https://doi.org/10.5256/f1000research.56487.r86525

Peter Nagy
Vadaskert Hospital and Outpatient, Budapest, Hungary

The authors address an important problem Tourette's experts face: by demonstrating how Tourette's syndrome (TS) is not in fact the rare curiosity people had long thought it to be, TS was actually removed from the category of rare diseases, stripping patients of the opportunities rare disease research could bring them. They argue that even though prevalence rates are higher than rare disease definition requirements, the number of patients, especially adult patients with a degree of impairment calling for treatment will be considerably lower, making this subgroup qualify for the rare disease category.

The need for intensive research is painfully obvious to experts of the field: with the enormous advances in research technologies over the past decades, it is almost embarrassing to admit that the "exact pathophysiology remains elusive" to this day (Cavanna, 2018), and it is then no surprise that we are far from being able to confidently offer safe and effective treatment options for our patients (the most recent AAN guideline found only moderate confidence for the efficacy of most therapies, except for CBIT, Pringsheim et al., 2019). However, the main argument (TS should be considered a rare disease) needs some careful consideration. It appears from the available data that TS based on its current definition is definitely not a rare disease, so, based on evidence, classifying the diagnosis *per se* as rare will not be possible. Careful and evidence-based definition of subgroups, however, as suggested by the authors, could be a useful route to take, but specific criteria based on evidence will need to be defined. Although for research on certain aspects, like pathogenesis, the rationale for excluding some more frequent presentations of the disorder (e.g. pediatric patients or patients without coprolalia and echolalia) seems difficult to support, the study of other aspects, like pharmacological treatment, will have to be limited to substantially smaller populations, very likely to hit rare disease definitions on one hand, and very unlikely to motivate companies to invest in such research on the other.

In conclusion, the accurate definition of evidence-based subgroups could be a promising way forward towards understanding and hopefully better treating this elusive, but very real and sometimes very impairing disorder.

References

1. Cavanna AE: The neuropsychiatry of Gilles de la Tourette syndrome: The état de l'art.*Rev Neurol*

(Paris). 2018; **174** (9): 621-627 PubMed Abstract | Publisher Full Text
2. Pringsheim T, Holler-Managan Y, Okun M, Jankovic J, et al.: Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology* . 2019; **92** (19): 907-915 Publisher Full Text

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neurodevelopmental disorders, psychopharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Jul 2021

Andreas Hartmann, Groupe Hospitalier Pitié-Salpétriére, Paris, France

We thank Dr Nagy for his thoughtful comments.

We agree that reclassifying TS is impossible or actually helpful. In the same vein, we have no wish to officially move TS into the rare disease category. However, we wish to alert the public and policy makers that, in real life, TS shares many features with rare diseases, i.e., a certain neglect and underfunding – especially when taking into account its prevalence, which represents a mismatch in our opinion. Therefore, benefitting from certain advantages inherent to rare diseases seems legitimate to us – for the time being. One example given is participating in the European Organization for Rare Diseases (EURORDIS) network, and apply for national or EU funding in this field.

As to the pharmaceutical industry, it would, as Dr Nagy points out, rather be demotivated to invest into research for TS if it was indeed rare (and again, it isn't based on prevalence), so that obtaining orphan drug status for TS cannot be considered neither an achievable or desirable aim.

However, we agree again with Dr Nagy that more research is needed in defining subgroups in TS; given the fluctuation in symptomatology, it would theoretically be quite possible for

an individual to be part of different subgroups within her lifetime! Especially adult TS remains very much of black box in terms of prevalence, evolution and long-term prognosis: here, major research efforts (longitudinal and epidemiological) are needed.

Competing Interests: No competing interests were disclosed.

Author Response 04 Oct 2021

Andreas Hartmann, Groupe Hospitalier Pitié-Salpétriére, Paris, France

We thank Dr Nagy for his thoughtful comments.

We agree that reclassifying TS might not be possible or actually helpful. In the same vein, we have no wish to officially move TS into the rare disease category. However, we wish to alert the public and policy makers that, in real life, TS shares many features with rare diseases, i.e., a certain degree of neglect and underfunding – especially when taking into account its prevalence, which represents a mismatch in our opinion. Therefore, benefitting from certain advantages inherent to rare diseases seems legitimate to us – for the time being. One example given is participating in the European Organization for Rare Diseases (EURORDIS) network, and applying for national or EU funding in this field.

As Dr Nagy points out, the pharmaceutical industry would be rather demotivated to invest into research for TS if it was indeed rare (and again, it isn't based on prevalence), so that obtaining orphan drug status for TS cannot be considered neither an achievable nor desirable aim.

However, we agree again with Dr Nagy that more research is needed in defining subgroups in TS; given the fluctuation in symptomatology, it would theoretically be quite possible for an individual to be part of different subgroups within her lifetime! Especially adult TS remains very much of black box in terms of prevalence, evolution, and long-term prognosis: here, major research efforts (both longitudinal and epidemiological) are needed. This point has been expanded and highlighted in the revised version of the manuscript, and two references added.

Competing Interests: No competing interests were disclosed.

Comments on this article

Version 1

Reader Comment (*F1000Research Advisory Board Member*) 02 Jun 2021

Kevin J Black, Washington University in St. Louis, St. Louis, Missouri, USA

Hartmann *et al*. make an important point here. I agree with their main argument, that Tourette

syndrome remains an orphan or neglected illness. They also correctly note that prevalence may fall into the "rare" range by focusing on those with "classic" features such as coprophenomena and echophenomena. Of course, most Tourette patients even in a specialty clinic setting do not have these features.

Other choices for limiting the illness definition are not ideal. Prevalence is lower for patients (*i.e.* those seeking treatment), though that choice would create varying prevalence in different settings for non-biological reasons, since treatment depends on societal variables such as availability of treatment. DSM–IV Tourette's Disorder, characterized by tics that impair patients' function in a life role or markedly distress them, also has lower prevalence, but one of the most rigorous epidemiological studies found a prevalence of 1.61% for TS with impairment in children 5-17 years old, still far from "rare".[1]

1. Cubo E et al. Prevalence of Tics in Schoolchildren in Central Spain: A Population-Based Study . Pediatric Neurology 45(2):100–108, 2011. DOI 10.1016/j.pediatrneurol.2011.03.003

Competing Interests: I have co-authored works with some of the authors.