Is Tourette syndrome a rare disease? [version 1; peer review: 1 approved, 1 approved with reservations]

Andreas Hartmann1, Natalia Szejko2,3, Nanette Mol Debes4, Andrea E. Cavanna5-7, Kirsten Müller-Vahl8

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

Abstract
Based on its prevalence, Tourette syndrome cannot be considered a rare disease. 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.
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 Health² 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 2002³ 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 Act⁵ 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 (EURORDIS⁶) 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 handicap 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.

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).

---
¹https://en.wikipedia.org/wiki/Rare_disease.
⁶www.eurordis.org.
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 sequelae, 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).

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. 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.
Open Peer Review

Current Peer Review Status: ✔️❓

[Image 269x671 to 287x689]
[Image 303x671 to 321x689]
[Image 29x649 to 580x650]
[Image 179x483 to 191x495]
[Image 58x479 to 76x497]

© 2021 Hedderly T et al. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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-occurring 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 sequelae, as mentioned in the viewpoint paper. We understand that potentially histaminergic, serotonergic, dopaminergic, glutaminergic genes and pathways are involved in the generation of tics and tic-like behaviour and in the co-occurring 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:


References

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-Salpêtrière, 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” or “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.
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

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-Salpêtrière, 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.

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 coprophrenomena 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


**Competing Interests:** I have co-authored works with some of the authors.
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com