Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis

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Declared competing interests of authors: Madeleine Groom reports grants from Shire Pharmaceuticals and personal fees from Janssen Pharmaceuticals outside the submitted work.

Published January 2016
DOI: 10.3310/hta20040

Scientific summary

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Health Technology Assessment 2016; Vol. 20: No. 4
DOI: 10.3310/hta20040

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Scientific summary

Background

Tourette syndrome (TS) is a neurodevelopmental condition characterised by chronic motor and vocal tics affecting up to 1% of school-age children and young people and is associated with significant distress and psychosocial impairment. The main treatments are pharmacological and behavioural interventions; however, little is known about their benefits and risks, how they are experienced by children and young people, and what treatment outcomes are most valued.

Objectives

To conduct a systematic review and meta-analysis of the benefits and risks of pharmacological, behavioural and physical interventions for tics in children and young people with TS (part 1), and to conduct a qualitative study of experiences of services and treatment to explore the experience of treatment and to understand which outcomes are most valued from the perspective of young people with TS and their parents (part 2).

Methods

Data sources

For the systematic reviews (parts 1 and 2), mainstream bibliographic databases (EMBASE, MEDLINE, PREMEDLINE In-Process & Other Non-Indexed Citations and PsycINFO), The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL) – Database of randomised controlled trials (RCTs) and other controlled trials], Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE) and Health Technology Assessment (HTA), education (e.g. British Education Index), social care (e.g. Applied Social Sciences Index and Abstracts) and grey literature (e.g. Health Management Information Consortium) databases were searched using subject headings and text words for tic and tourette from database inception (or 1995 for part 2) to January 2013.

For part 2, additional data were collected from two sources (1) an online national survey hosted via the Tourettes Action website (www.tourettes-action.org.uk/) of the experiences of care and treatment of parents of children and young people with TS (aged $\leq$ 17 years), and (2) in-depth qualitative interviews with young people with TS (aged 11–17 years) to explore their experiences of care and treatment.

Study selection

For part 1, results were screened for RCTs and controlled before-and-after studies of pharmacological, behavioural or physical interventions in children or young people (aged $<$ 18 years) with TS or chronic tic disorder. Studies in adults or mixed populations were considered as supporting evidence.

For part 2, results were screened for qualitative systematic reviews, qualitative studies and survey literature of access to and experience of care for young people with TS. Results for the quantitative searches (part 1) were also screened for any relevant studies.

Data extraction and synthesis

For part 1, the critical outcome for the review was tic severity/frequency. Data were abstracted by one reviewer and checked by a second. The Cochrane risk of bias tool was used for the risk of bias assessment and the Grading of Recommendations Assessment, Development and Evaluation approach for assessing the overall quality of the evidence.

For part 2, results are presented under theme headings, to group information from different studies on similar outcomes or themes. Related participant quotations are presented to illustrate the themes but no exploration or synthesis of the original quotes from the primary study was performed.

Results

For part 1, of 6345 citations screened, 70 studies were included in the quantitative systematic review. The main review findings suggest:

- There is clear evidence that antipsychotics [standardised mean difference (SMD) –0.74, 95% confidence interval (CI) –1.08 to –0.41; $n = 75$] and noradrenergic agents [clonidine (Dixarit®, Boehringer Ingelheim) and guanfacine] (SMD –0.72, 95% CI –1.03 to –0.40; $n = 164$) produce improvements in tics that may be clinically meaningful in children and young people with TS. The quality of the evidence was generally low.
- The available evidence suggests that there are unlikely to be important clinical differences in tic reduction among antipsychotics and between antipsychotics and noradrenergic agents. There is no clear evidence that the clinical effectiveness of antipsychotics or noradrenergic agents is moderated by either tic severity or comorbidity.
- There is evidence that, in the short term, neither stimulants and atomoxetine (Strattera®, Lilly) (used to treat comorbid TS and attention deficit hyperactivity disorder) nor fluoxetine (Prozac®, Lilly) (used to treat comorbid TS and obsessive–compulsive disorder) significantly exacerbate or worsen tics, but atomoxetine may reduce tics. The quality of the evidence was generally very low.
- Topiramate (Topamax®, Janssen), pergolide, metoclopramide (Maxolon®, AMCo) and desipramine are other agents with evidence that suggests they may be effective in reducing tics. However, the known adverse effect profiles of these drugs, balanced against relatively weak poor-quality evidence of benefits, means that these agents are unlikely to be considered clinically useful for treating tics.
- A number of other agents were reviewed and were found not to be clinical effective for treating tics: levetiracetam (Keppra®, UCB Pharma), selegiline (Eldepryl®, Orion; Zelapar®, TEVA UK), pramipexole (Mirapexin®, Boehringer Ingelheim), mecamylamine (Inversine®, Targacept Inc.), ondansetron (Zofran®, GSK), baclofen (Lioresal®, Novartis), omega-3 fatty acids and transdermal nicotine patches. The quality of the evidence was generally low.
- There is clear evidence that habit reversal training (HRT)/comprehensive behavioural intervention for tics (CBIT) produces improvements in tics that may be clinically meaningful (SMD –0.64, 95% CI –0.99 to –0.29; $n = 133$). There is no evidence that the effects of HRT/CBIT are moderated by tic severity. The quality of the evidence was moderate to low.
- There is some preliminary evidence that delivering HRT/CBIT remotely via video consultation (telemedicine) may be as effective as face-to-face therapy. The quality of the evidence was low.
- There are no RCTs of negative (massed) practice or exposure and response prevention (ERP) compared with control interventions. However, head-to-head comparisons suggest that HRT is a more effective intervention than negative practice, while HRT and ERP may be equally effective interventions for tics. The quality of evidence for interventions other than HRT/CBIT is low and so conclusions drawn from this evidence should be treated with caution.
- There is no conclusive evidence that relaxation therapy in isolation is an effective treatment for tics. Anger control training may be a useful intervention for young people with tics and comorbid disruptive behaviour and behaviour problems may be improved by parent training, although there is no conclusive evidence that parent training is an effective treatment for tics. The quality of the evidence was generally very low.

- There is no robust evidence to suggest that the physical interventions reviewed [deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), intravenous (i.v.) immunoglobulin, botulinum toxin and acupuncture] are sufficiently effective and safe to be considered as treatments for tics in children and young people with TS.
- There is no conclusive evidence that i.v. immunoglobulin or penicillin are effective treatments for tics in children and young people identified with Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS). The quality of the evidence was low.
- There is a high degree of uncertainty with respect to the benefits and harms of plasma exchange in the treatment of tics in children and young people identified with PANDAS. The quality of the evidence was generally very low.

For part 2, four studies were included in the qualitative systematic review. For the online survey, 358 parents from across the UK consented to complete the online survey and useful data were analysed from 295 respondents. The majority of respondents were mothers (92.2%) and the mean age of their child with TS was 12.4 years [standard deviation (SD) 3.0] and 79.3% of the children were male. The mean age of onset of tics was 5.9 years (SD 2.8) and mean age at diagnosis of TS was 9.1 years (SD 2.7). For the in-depth interviews, 40 young people with TS, median age 13.0 (range 10–17 years) were interviewed; 31 (77.5%) were male. Main research findings and themes:

- The online national survey found that just over half of young people with TS had received medication for tics. The most commonly used drugs were risperidone (Risperdal®, Janssen), clonidine and aripiprazole (Abilify®, Otsuka).
- Young people and parents reported that medication could be helpful in reducing tics but frequently expressed concerns about adverse effects and lack of provision of relevant information explaining the rationale for using medication for tics and possible adverse effects.
- Of the medications surveyed, parents of young people with TS perceived aripiprazole as being most helpful with least troublesome adverse effects.
- The online national survey found that about one-quarter of young people with TS had received a behavioural intervention (broadly conforming to HRT/CBIT) for tics. Behavioural interventions were almost always delivered together with medication.
- Young people with TS and parents reported that behavioural interventions (HRT/CBIT) could be helpful in reducing tics and adverse effects were rarely reported. Young people reported that they valued the opportunity to learn behavioural techniques that helped them control tics and build on strategies that they had developed themselves. However, some young people found these approaches difficult to use and were not always helpful.
- Young people with TS and their parents frequently reported concerns about lack of knowledge of TS and its treatment among health professionals both in primary care (general practitioners) and secondary care [child and adolescent mental health services (CAMHS) and paediatrics].
- Delays in recognition and referral for diagnosis were common with the average delay of 3 years from onset of tics to diagnosis of TS.
- Young people with TS and their parents placed great emphasis on the provision of information about TS and its management. Often this information was not provided by health services or was viewed as inadequate. An important finding was the lack of information provided by health services to schools on TS and its management. In only one-quarter of children and young people with TS surveyed had health professionals contacted and provided information to the school.
- Young people with TS and their parents highlighted the importance of recognising and managing anxiety symptoms associated with TS.
- Young people with TS and their parents regarded reducing the frequency and intensity of tics and increasing control over tics as the most important outcomes of treatment.
- Reducing anxiety and stress associated with tics was viewed by young people in particular as important.

Limitations

The number and quality of clinical trials is low and this downgrades the strength of the evidence and conclusions. In the qualitative study, lack of information on dosing and comparison with a control intervention means that findings relating to the experience of treatment cannot be interpreted as evidence of effectiveness or lack of harm.

Conclusions

The findings of this systematic review and evidence synthesis show that there are effective pharmacological (e.g. antipsychotics and noradrenergic agents) and behavioural interventions (e.g. HRT/CBIT) available for the treatment of tics in children and young people with TS. However, the number and quality of clinical trials is low and this downgrades the strength of the evidence and conclusions. Larger and better-conducted trials addressing important clinical uncertainties are required. Key themes from the qualitative study were difficulties in access to specialist care, delay in diagnosis, importance of anxiety and emotional symptoms in TS, lack of provision of information to schools and inadequate information regarding medication and adverse effects. Of the medications surveyed, parents of young people with TS perceived aripiprazole as being most helpful with least troublesome adverse effects. Only one-quarter of young people in the national online survey, and less than one-fifth of young people interviewed, reported having received an evidence-based behavioural intervention (HRT/CBIT) for tics. The perspective of young people with TS and their parents on their experience of treatment and care have received little research attention. Therefore, these findings should lay the foundations for future research and contribute to the development of patient-centred treatment guidelines.

Implications for health care

Access to behavioural interventions is currently limited and delay in diagnosis of TS was on average 3 years from symptom onset. Knowledge of TS and its management among health professionals is often inadequate and information provision to schools is generally poor. Those working in primary care should be aware of the prevalence and clinical features of children and young people presenting with tics and suspected TS. There appears to be a lack of clear care pathways and inadequate care may result from a lack of integration in the commissioning and provision of physical and mental health services. Care pathways for children with suspected TS need to be established to accelerate access to expert assessment and diagnosis. It is important that health commissioners recognise that local CAMHS should provide assessment and treatment of TS and also offer referral and support for patients who need to access specialist centres. Information packages for schools should be developed and evaluated. The relevance of associated anxiety and emotional symptoms is often overlooked and requires greater attention from both clinical practice and research. This is a complex issue as anxiety can be both a cause and consequence of tics and is also related to premonitory urges.

Recommendations for research

Further research is needed to inform the development of clinical guidelines for children and young people with TS, in particular to answer questions about the order in which interventions should be given, how interventions should be combined and how their clinical effectiveness and cost-effectiveness is affected by comorbidity and tic severity. Aripiprazole was perceived by parents of young people with TS as the most helpful medication with a relatively favourable adverse effect profile. However, lack of information on dosing and comparison with a control intervention means that this cannot be interpreted as evidence of effectiveness or lack of harm. Currently, there are no placebo-controlled studies available for aripiprazole in the treatment of tics, although trials may be ongoing. Therefore, evidence from controlled trials is needed for aripiprazole before firm conclusions regarding its efficacy and safety can be drawn.

Health services research is required to identify barriers to care and unmet needs for services for young people with TS and to develop targeted interventions to improve referral practice and reduce the delay between onset of tics and diagnosis. Poor access to behavioural interventions is an important issue and research is needed to test whether or not technological innovations (e.g. mobile digital and video technology) can be used to widen access, reduce the cost and face-to-face duration of therapy while maintaining the effectiveness of the intervention.

Finally, tic reduction is a relevant primary outcome for both clinical practice and research trials and current measures such as the Yale Global Tic Severity Scale should continue to be used. Secondary outcomes should include reduction in associated anxiety, stress and improved self-esteem.

Key research questions and priorities

1. Is the combination of a behavioural intervention together with medication management more clinically effective and cost-effective in the short term than either behavioural intervention alone or medication management alone for the treatment of moderate and severe tics in children and young people with TS?
2. What is the feasibility, acceptability, clinical effectiveness and cost-effectiveness of a behavioural intervention for tics that is delivered remotely [e.g. via telemedicine/videoconference or Skype™ (Microsoft Corporation, Redmond, WA, USA)] compared with traditional face-to-face delivery of therapy?
3. What is the feasibility, acceptability, clinical effectiveness and cost-effectiveness of a behavioural intervention (HRT/CBIT) and self-monitoring mobile application (‘app’) for tics compared with traditional face-to-face delivery of therapy?

Study registration

The study is registered as PROSPERO CRD42012002059.

Funding

The National Institute for Health Research HTA programme.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/142/01. The contractual start date was in June 2012. The draft report began editorial review in August 2013 and was accepted for publication in August 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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