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Practitioner Review: Treatments for Tourette syndrome in children and young people – a systematic review

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Background: Tourette syndrome (TS) and chronic tic disorder (CTD) affect 1–2% of children and young people, but the most effective treatment is unclear. To establish the current evidence base, we conducted a systematic review of interventions for children and young people. **Methods:** Databases were searched from inception to 1 October 2014 for placebo-controlled trials of pharmacological, behavioural, physical or alternative interventions for tics in children and young people with TS or CTD. Certainty in the evidence was assessed with the GRADE approach. **Results:** Forty trials were included [pharmacological (32), behavioural (5), physical (2), dietary (1)]. For tics/global score there was evidence favouring the intervention from four trials of α2-adrenergic receptor agonists [clonidine and guanfacine, standardised mean difference (SMD) = −0.71; 95% CI −1.03, −0.40; N = 164] and two trials of habit reversal training (HRT)/comprehensive behavioural intervention (CBIT) (SMD = −0.64; 95% CI −0.99, −0.29; N = 133). Certainty in the effect estimates was moderate. A post hoc analysis combining oral clonidine/guanfacine trials with a clonidine patch trial continued to demonstrate benefit (SMD = −0.54; 95% CI −0.92, −0.16), but statistical heterogeneity was high. Evidence from four trials suggested that antipsychotic drugs improved tic scores (SMD = −0.74; 95% CI −1.08, −0.40; N = 76), but certainty in the effect estimate was low. The evidence for other interventions was categorised as low or very low quality, or showed no conclusive benefit. **Conclusions:** When medication is considered appropriate for the treatment of tics, the balance of clinical benefits to harm favours α2-adrenergic receptor agonists (clonidine and guanfacine) as first-line agents. Antipsychotics are likely to be useful but carry the risk of harm and so should be reserved for when α2-adrenergic receptor agonists are either ineffective or poorly tolerated. There is evidence that HRT/CBIT is effective, but there is no evidence for HRT/CBIT alone relative to combining medication and HRT/CBIT. There is currently no evidence to suggest that the physical and dietary interventions reviewed are sufficiently effective and safe to be considered as treatments. **Keywords:** Paediatrics; Tourette syndrome; therapy; tics.

Introduction

Tourette syndrome (TS) and chronic tic disorder (CTD), characterised by the presence of combined or singular motor and phonic tics, have their onset in childhood, typically around the age of 6 or 7 years (Jin et al., 2005; Leckman et al., 1998) with tics at their worst between the ages of 8 and 12 years (Leckman et al., 1998). The prevalence in children has been estimated as 0.4%–0.7% (Jin et al., 2005; Khalifa & von Knorring, 2005; Kraft et al., 2012; Scharf, Miller, Mathews, & Ben-Shlomo, 2012) for TS and 0.6%–1.3% (Khalifa & von Knorring, 2005; Kraft et al., 2012; Scharf, Miller, Mathews, & Ben-Shlomo, 2012) for CTD (1% prevalence overall). In general, tics wane in severity in late adolescence and early adult life (Burd et al., 2001; Kraft et al., 2012; Leckman et al., 1998), and in adulthood prevalence is lower (Schlander, Schwarz, Rothenberger, & Roessner, 2011). TS is frequently comorbid with other psychiatric conditions including attention-deficit hyperactivity disorder (ADHD; 60%), anxiety disorder (40%), obsessive compulsive disorder/obsessive compulsive behaviours (OCD/OCB; 30%) and autism spectrum disorder (ASD; 20%) (Robertson, 2015). Carers of children with TS experience considerable burden and risk of psychological morbidity (Cooper, Robertson, & Livingston, 2003) and children with tic disorders experience high rates of social (Kraft et al., 2012; Wadman, Tischler, & Jackson, 2013), emotional (Kraft et al., 2012; Robertson, Banerjee, Eapen, & Fox-Hiley, 2002) and educational (Debes, Hjalgrim, & Skov, 2010) impairment, and experience a lower quality of life (Eddy et al., 2011).

Considering the nature of tic-related impairments and implications for future life, knowledge of the best

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treatment options for TS in children is clinically important. Detection and treatment of the psychiatric comorbidities which occur in the majority of children with tics/TS may also be a clinical priority. However, in many children, attempting to reduce the severity, frequency, intensity and impact of tics is a significant therapeutic target, and children and parents report the importance of tic reduction (Cuenca et al., 2015). Current practice varies between countries but, following a course of psychoeducation (Robertson, 1989), where further treatment is indicated, the most widespread mode of treatment is pharmacotherapy. Commonly used medications are antipsychotics, such as risperidone and aripiprazole, or the α2-adrenergic receptor agonists clonidine and guanfacine (Debes, Hjalgrim, & Skov, 2009; Rickards, Cavanna, & Worrall, 2012). Behavioural therapies, such as habit reversal training (HRT) and exposure and response prevention (ERP), are used less often (Verdellen, van de Griendt, Hartmann, Murphy, & ESSTS Guidelines Group). This is often due to a lack of availability, financial constraints or both. Physical treatments such as repetitive transcranial magnetic stimulation (rTMS) and, in adults, deep brain stimulation (DBS) (Muller-Vahl et al., 2011; Steeves et al., 2012), have been used with some success and reported in small case series, although it is acknowledged that adequately powered randomised trials are necessary. Alternative treatments such as fish oils, dietary supplements, chiropody, yoga, acupuncture and antibiotics (Debes et al., 2009; Kompoliti, Fan, & Leurgans, 2009; Woods, Conelea, & Himle, 2010) have also been used for tics, but the rationale for their use and efficacy of these treatments is unclear.

Comprehensive systematic reviews and meta-analyses of treatments for tics in children and young people with TS and CTD are lacking. Although there have been systematic reviews considering separately pharmacological (Waldon, Hill, Termine, Balottin, & Cavanna, 2013) and behavioural (Dutta & Cavanna, 2013; Wile & Pringsheim, 2013) interventions and a number of narrative reviews underpinning clinical guidelines (Muller-Vahl et al., 2011; Pringsheim et al., 2012; Roessner et al., 2011; Steeves et al., 2012; Verdellen, van Griendt, Hartmann, & Murphy, 2011), none have made an overall assessment of the evidence for all types of treatment and attempted to estimate the magnitude of benefits and harms and robustly assess the quality of the evidence. A number of reviews (McGuire et al., 2014; Weisman, Qureshi, Leckman, Scahill, & Bloch, 2013) have combined the effects of treatment in children and adult studies. This is unsatisfactory given that we know that children and adults can differ in important ways both in terms of the efficacy of treatments (Thapar, Collishaw, Pine, & Thapar, 2012) and susceptibility to adverse effects (NCCMH, 2013). A further justification for this review is the lack of systematic evidence-based clinical guidance for the treatment of tics in children and young people. In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has produced Clinical Guidelines for a range of childhood mental health conditions, but so far it has not produced a guideline for the management of young people with Tourette syndrome despite the prevalence and impairment associated with the condition. As a result, practitioners are left to draw clinical inferences from a small set of narrative and systematic reviews that typically focus on separate modalities of treatment, apply different standards of evidence and include different populations of patients. The current review aimed to improve upon past studies and establish the magnitude of both benefits and harms associated with pharmacological, behavioural, physical and alternative treatments for tics in children (aged < 18 years) with a clinical diagnosis of TS or CTD, when compared with a control group.

Methods

We partially updated an evidence synthesis conducted for the NIHR Health Technology Assessment programme (Grant Ref: 10/142/01). Study eligibility criteria and the analysis plan (including intervention classification scheme) were agreed by all authors before data extraction began (Hollis et al., 2016). The original review protocol was registered online with the International Prospective Register of Systematic Reviews in March 2012 (Registration number: CRD42012002059) and can be accessed at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002059. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for performing and presenting the present review.

Data sources

Twenty-one databases covering medical/health (e.g. Medline, CENTRAL, PsycINFO), education (e.g. ERIC), social care (e.g. Social Services Abstracts) and grey literature (e.g. Health Management Information Consortium) topics were searched for studies in any language. Searches were conducted from database inception to 1st January 2013 and updated in October 2014. The search strategy included key words (tic or tics or tourette$) and relevant subject headings (see Supporting Information for more information about the databases and search strategy). Citations were screened by one reviewer (MP) and hard copies of potentially relevant studies were obtained. The list of both included and excluded studies were screened by all authors and disagreements about eligibility were discussed.

Eligibility criteria

Inclusion and exclusion criteria were formulated using the PICO framework:

Patient/population. Aged <18 years old with a clinical diagnosis of TS or CTD. Those with a transient tic disorder (duration less than 12 months) were excluded. Studies where the upper age included 18 year olds were allowed given that all of these had a mean of between 10 and 14 years old.

Intervention. Pharmacological interventions[1] (including antipsychotic drugs, clonidine, tetrabenazine, fluoxetine, clonazepam)

and dietary interventions (including zinc, omega 3 fatty acids, caffeine) used for the treatment of tics, or psychological/behavioural and psychosocial interventions [including habit reversal training (HRT), comprehensive behavioural intervention for tics (CBIT), ERP, counselling and supportive psychotherapy, family interventions, psychoeducation, relaxation training, self-hypnosis, cognitive behavioural therapy and exercise) or other physical interventions (including neuro-therapeutic interventions, such as transcranial magnetic stimulation, and other physical interventions, such as acupuncture and botulinum toxin injection) used for any reason.

Comparison. Placebo, treatment as usual or other minimally active control. Head-to-head studies were excluded.

Outcome. Tic severity/frequency, or if not available, global scores (including tic and impairment subscales) or motor tic score.

Only randomised controlled trials (RCTs) or controlled before–after studies were eligible. For some interventions, only studies in mixed samples of children and adults were identified. Initially, authors were contacted and, where data from a subgroup of children were available, these were included in the review. Where subgroup data were not available, mixed studies in children and adults were used as evidence. Decisions about eligibility and classification of interventions were agreed by all authors before data were extracted. With regard to clonidine, it was decided that patches should be analysed separately from oral clonidine as there was a high risk of heterogeneity between these trials. However, we also conducted a post hoc analysis by combining data from trials of oral clonidine with clonidine patch trial data.

Data extraction and synthesis

Data were extracted by one reviewer and checked by a second reviewer using a prepiloted Excel-based form. Where numerous scales were reported, priority was given to the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) since this was the most commonly reported scale and is currently in common use. The Cochrane risk of bias tool was used to assess risk of bias in included studies (Higgins & Green, 2011). Additionally, for cross-over trials, the adequacy of the washout period between treatments was considered to inform the risk of bias assessment. The overall risk of bias for each study was assessed on the basis of whether any source of bias was likely to have had a significant impact on the findings (not simply based on a count of the number of sources of bias). The GRADE approach was used to assess certainty in the effect estimates (quality of evidence) for each outcome (Guyatt, Oxman, Schunemann, Tugwell, & Knottnerus, 2011) by one author (MP) and confirmed by CW. Any disagreements were discussed with other authors and consensus reached. The GRADE approach is a structured method that takes into consideration five separate factors: risk of bias; inconsistency (defined as important heterogeneity with an I^2 value that was statistically significant and greater than 50%); indirectness of the population, intervention, control or outcomes; imprecision (number of participants less than the optimum information size, assumed to be 300 events across dichotomous outcomes and total number of participants of 400 across continuous outcomes); and publication bias. Certainty in the effect estimates was categorised as 'high' (very certain that the true effect lies close to that of the estimate of the effect); 'moderate' (moderately certain in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); 'low' (certainty in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); or 'very low' (very little certainty in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) (Balshem et al., 2011). Using the GRADE approach, evidence from RCTs is initially classed as 'high', but may be rated down one or two levels on the basis of any of the five factors listed above.

Following the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011), we combined data from two or more individual trials using the computer program Review Manager (RevMan, version 5.3.; The Nordic Cochrane Centre, The Cochrane Collaboration 2014, Copenhagen, Denmark) using a random-effects model. For outcomes measuring benefit of treatment, the standardised mean difference (SMD) was used as the effect size, calculated as the difference in mean change scores divided by the pooled standard deviation of the change scores. Hedges' g correction for small sample size was applied automatically by RevMan. The SMD was standardised so that a negative effect size indicated that that the outcome favoured the intervention relative to the control. For trials where appropriate data were not directly reported, p values for the net effect, if available, were used to calculate the SMD and corresponding standard error (*SE*). In order to estimate the precision of within-group changes where only baseline and post-treatment means and standard deviation (*SD*) were reported, a correlation coefficient of 0.6 was assumed (median score found in studies reporting baseline, post-treatment and change scores where correlation coefficient could be determined). For cross-over studies, data were analysed as a comparison between post-treatment measures. Dichotomous data from adverse effect outcomes were expressed as a risk ratio (RR) and 95% CI.

Results

After removal of duplicate records, the search identified 6,345 citations and, of these, 223 were obtained for full-text screening (Figure 1). Forty trials in children or mixed studies (where children studies were not available for a particular intervention), published from 1987 to 2013 met eligibility criteria (a list of all excluded studies is available from the authors on request). Types of interventions and number of trials are shown in Table 1. Of the 40 included trials, 32 were of pharmacological interventions, 5 of behavioural interventions, 2 of physical interventions and 1 of a dietary intervention.

The characteristics of included trials are shown in Table 2 (pharmacological and dietary interventions) and Table 3 (behavioural and physical interventions). All interventions were given to participants with TS or CTD and aimed at tics or comorbid conditions (i.e. ADHD, OCD or ODD and incorporating a measure of tic frequency/severity as an outcome). Of the 40 included trials, four included mixed samples (children and adults); one study each of topiramate (Jankovic, Jimenez-Shahed, & Brown, 2010), IV immunoglobulin (Hoekstra, Minderaa, & Kallenberg, 2004), Botulinum toxin (Marras, Andrews, Sime, & Lang, 2001) and clonidine (Leckman et al., 1991). The Leckman et al. study was not the only trial of clonidine and therefore could have been excluded based on our eligibility criteria. However, the mean age was approximately 15 years and only 23% of the sample were 18 years or older. Therefore, it was decided to include this trial.

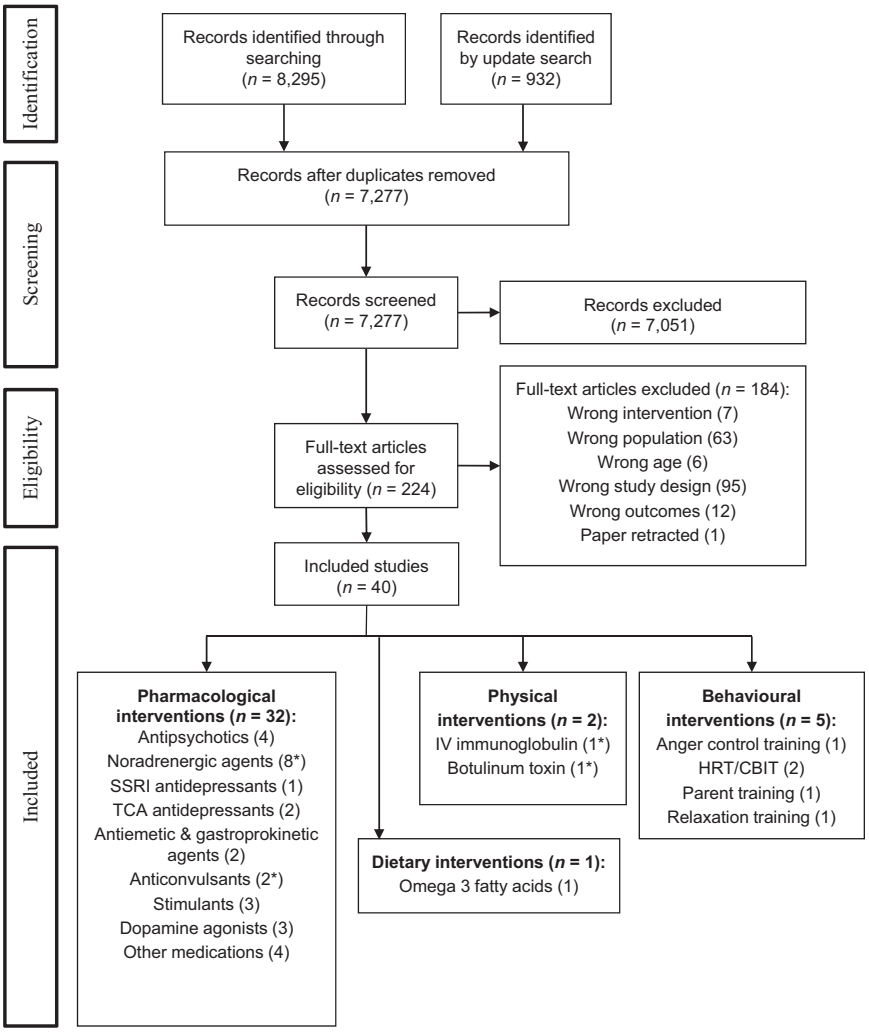

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (the number of studies is shown in parentheses; numbers marked with an asterisk include at least one mixed study of children/young people and adults)

It should be noted that all trials that were excluded on the basis of age had a mean age above 18, with the majority of participants being adults.

The evidence for selected benefits and important harms associated with each intervention, and the GRADE assessment of certainty in the effect estimates are shown in Table 4. A graphical display of the main outcome (benefit) for each intervention subgrouped by GRADE category can be found in Figure 2. Outcomes were mostly graded as low or very low, but for a small number of interventions, there was moderate certainty in the evidence (no evidence with high certainty was identified).

Pharmacological interventions

Interventions with moderate certainty in the estimates of effect. There was evidence from pooling the results of four trials (total sample size, $N = 164$) that α adrenergic receptor agonists (clonidine and guanfacine) had a medium-sized benefit on tic/global score (SMD = −0.74; 95% CI −1.06, −0.42; $I^2 = 0\%$; heterogeneity $p = 1.00$). There was evidence from one large trial ($N = 437$) that failed to show a benefit of clonidine patch on tics (SMD = −0.10; 95% CI −0.32, 0.12). A post hoc analysis combining oral clonidine/guanfacine and clonidine patch produced a medium-sized benefit on tic/global score (SMD = −0.54; 95% CI −0.92, −0.16), but statistical heterogeneity was high ($I^2 = 63\%$; heterogeneity $p = .03$). Based on one relatively large trial ($N = 145$) there was evidence that atomoxetine had a positive effect on tics, but the estimate of effect was imprecise (SMD = −0.32; 95% CI −0.65 to 0.01).

Interventions with low or very low certainty in the estimates of effect. There was evidence from pooling the results of four trials that antipsychotic drugs improved tics (SMD = −0.78; 95% CI −1.13, −0.43; $N = 136$). There was no evidence of important differences between specific antipsychotic drugs in the size of the effect ($I^2 = 0\%$; heterogeneity $p = .74$): aripiprazole (SMD = −0.62), haloperidol (SMD = −0.50), pimozide (SMD = −0.81), risperidone (SMD = −1.18) and ziprasidone (SMD = −0.74). There was evidence from one trial of each drug that metoclopramide (SMD = −1.43; 95% CI −2.28, −0.59; $N = 27$), desipramine (SMD = −0.96; 95% CI −1.63,

Table 1 Number of articles providing data for each intervention, categorised by type of intervention

Intervention	Number of studies
Pharmacological interventions	
α2-adrenergic receptor agonists	
Clonidine	4[a]
Clonidine patch	2
Guanfacine	2
Antihypertensive	
Mecamylamine	1
Antidepressants (SSRI)	
Fluoxetine	1
Antidepressants (TCA)	
Desipramine	2
Antiemetics	
Metoclopramide	1
Ondansetron	1
Anticonvulsants	
Levetiracetam	1
Topiramate	1[a]
Antiparkinsonian agents	
Selegiline	1
Antipsychotics	
Aripiprazole	1
Haloperidol	1
Pimozide	1
Risperidone	1
Ziprasidone	1
CNS stimulants	
Methylphenidate	3
Dopaminergic agents	
Pergolide	2
Pramipexole	1
Muscle relaxants	
Baclofen	1
Smoking cessation agents	
Nicotine patch	1
Selective norepinephrine reuptake inhibitor	
Atomoxetine	1
Dietary interventions	
Omega 3 fatty acids	1
Behavioural interventions	
Anger control training	1
HRT/CBIT	2
Parent training	1
Relaxation training	1
Physical interventions	
Botulinum toxin	1[a]
IV immunoglobulin	1[a]
Total number of studies	40

[a]Mixed sample of children/young people and adults.

−0.29; $N = 39$) and topiramate (SMD = −0.88; 95% CI −1.68, −0.08; $N = 27$) improved tics. There was some evidence from one trial of each drug that selegiline (SMD = −0.72; 95% CI −1.45, 0.02; $N = 15$) and pergolide (SMD = −0.59; 95% CI −1.21, 0.02; $N = 51$) may improve tics. The evidence from one trial of each drug was inconclusive regarding the benefit of levetiracetam (SMD = −0.23; 95% CI −0.85, 0.39; $N = 40$) and pramipexole (SMD = 0.00; 95% CI −0.53, 0.53; $N = 62$). For other medications, evidence from one trial for each drug was inconclusive: baclofen (SMD = −0.54; 95% CI −1.50, 0.42; $N = 9$), fluoxetine (SMD = −0.90; 95% CI −2.15, 0.34; $N = 11$) and ondansetron (SMD = −0.38; 95% CI −1.42, 0.66; $N = 15$). For CNS stimulants, the important finding from four trials was that they did not appear to worsen tics (SMD = −0.17; 95% CI −0.45, 0.11; $N = 161$).

Harms associated with treatment. Given the relatively small sample sizes and small number of trials for each drug, we focus here on any evidence of increased overall adverse effects and any serious adverse effects reported. In one trial of oral clonidine, there was an increased risk of adverse effects (RR = 1.87; 95% CI 1.24, 2.81). With regard to antipsychotic drugs, there was evidence that only haloperidol increased extrapyramidal symptoms when compared to placebo (SMD = 0.51; 95% CI 0.11, 0.90; $N = 22$). In one trial of desipramine (TCA antidepressant), there was an increased risk of adverse effects (RR = 1.73; 95% CI 1.14, 2.64).

Dietary interventions

In one small trial ($N = 33$) of omega 3 fatty acids, the evidence was inconclusive regarding the effect on tics (SMD = −0.24; 95% CI −0.93, 0.45). Certainty in the effect estimate was low.

Behavioural interventions

Interventions with moderate certainty in the estimates of effect. When the results of two trials ($N = 133$) were pooled, there was evidence of a medium-sized effect in improving tics in favour of behavioural therapy (HRT/CBIT) when compared to waitlist/supportive psychotherapy (SMD = −0.64; 95% CI −0.99, −0.29; $I^2 = 0\%$; heterogeneity $p = .94$).

Interventions with low or very low certainty in the estimates of effect. Evidence for other behavioural interventions, from one trial each, was inconclusive: anger control training (SMD = −0.58; 95% CI −1.37, 0.20; $N = 26$), parent training (SMD = 0.29; 95% CI −0.53, 1.12; $N = 23$) and relaxation training (SMD = −0.61; 95% CI −1.76, 0.54; $N = 16$).

Physical interventions

Evidence from one trial for each intervention was inconclusive as to the benefit of botulinum toxin (SMD = 0.02; 95% CI −0.63, 0.67; $N = 18$) and IV immunoglobulins (SMD = −0.51; 95% CI −1.25, 0.23; $N = 29$) on tics. Certainty in the effect estimates was low. In the trial of IV immunoglobulins, there was an increased risk of adverse effects (RR = 3.48; 95% CI 1.49, 8.16). There was no evidence for DBS or rTMS in children or in mixed children and adult studies.

Table 2 Characteristics of included trials assessing pharmacological and dietary interventions for Tourette syndrome

Treatments	Study	Design	*N*	Age: mean (*SD*); range	Duration (weeks)	Diagnosis (comorbid diagnosis)	Mean dose (*SD*)	Attrition
α2-adrenergic receptor agonists								
Clonidine versus PLB	Kurlan et al. (2002)	Parallel RCT (4-arm trial)	66	10.2 (2.0); 7–14	16	94% TS 6% CTD (100% ADHD, 16% OCD)	0.25 mg/day (NR)	89% completed 100% analysed
Clonidine versus PLB	Goetz, Tanner, and Wilson (1987)	Cross-over RCT	24	12.9 (2.6); 8–17	6	100% TS (8% ADHD, 8% OCD)	0.015 mg/kg/day (NR)	NR
Clonidine versus PLB	Leckman et al. (1991)	Parallel RCT	47	15.6 (10.4); 7–48[a]	12	100% TS (55% ADHD, 20% OCD)	4.4 ug/kg/day (0.7)	89% completed 85% analysed
Clonidine versus PLB	Singer et al. (1995)	Cross-over RCT	37	10.6 (NR); 7–14	6	100% TS (100% ADHD, NR% OCD)	0.2 mg/day (NR)	92% completed 92% analysed
Clonidine patch versus PLB patch	Du et al. (2008)	Parallel RCT	437	10.1 (2.8); 6–18	4	55% TS 40% CTD (NR% ADHD/OCD)	1–2 mg/day for body weight <20–60 kg (NR)	87% completed 100% analysed
Clonidine patch versus PLB patch	Zhong, Zhou, and Hu (2007)	Parallel RCT	76	9 (NR); 6–18	4	100% TS (NR% ADHD/OCD)	1–2 mg/day for body weight <20–60 kg (NR)	NR
Guanfacine versus PLB	Cummings, Singer, Krieger, Miller, and Mahone (2002)	Parallel RCT	24	10.4 (2.3); NR	4	96% TS 4% CTD (100% ADHD, NR% OCD)	2.0 mg/day (NR)	NR
Guanfacine versus PLB	Scahill et al. (2001)	Parallel RCT	34	10.4 (2.0); 7–14	8	59% TS 35% CTD	2.5 mg/day (NR)	NR
Antihypertensives								
Mecamylamine versus PLB	Silver, Shytle, Sheehan et al. (2001)	Parallel RCT	61	11.3 (NR); 8–17	8	100% TS (60% ADHD, 30% OCD)	7.5 mg/day (NR)	62% completed 82% analysed
Antidepressants (SSRI)								
Fluoxetine versus PLB	Kurlan, Como, Deeley, McDermott, and McDermott (1993)	Parallel RCT	11	13.1 (2.6); 10–18	28	100% TS (NR% ADHD, 100% OCD)	40 mg/day (NR)	82% competed 82% analysed
Antidepressants (TCA)								
Desipramine versus PLB	Spencer et al. (2002)	Parallel RCT	39	10.9 (3.0); NR	6	87% TS 13% CTD (100% ADHD, 29% OCD)	3.4 mg/kg/day (0.3)	95% completed 100% analysed
Desipramine versus PLB	Singer et al. (1995)	Cross-over RCT	37	10.6 (NR); 7–14	6	100% TS (100% ADHD, 0% OCD)	100 mg/day (NR)	92% completed 92% analysed
Antiemetics								
Metoclopramide versus PLB	Nicolson, Craven-Truss, Smith, McKinlay, and Castellanos (2005)	Parallel RCT	27	11.5 (2.6); 7–18	8	96% TS 4% CTD (67% ADHD, NR% OCD)	32.9 mg/day (5.1)	86% completed 96% analysed
Ondansetron versus PLB	Toran, Weizman, Ratner, Cohen, and Laor (2005)	Parallel RCT	15	14.0 (2.9); 12–18	3	100% TS (20% ADHD, 13% OCD)	24 mg/day (NR)	87% completed 87% analysed
Anticonvulsants								
Levetiracetam versus PLB	Smith-Hicks, Bridges, Paynter, and Singer (2007)	Cross-over RCT	22	12.2 (2.3); 8–16	4	100% TS (50% ADHD, 9% OCD, 45% OCD behaviours)	30 mg/kg/day (NR)	91% completed 91% analysed

Table 2 (continued)

Treatments	Study	Design	*N*	Age: mean (*SD*); range	Duration (weeks)	Diagnosis (comorbid diagnosis)	Mean dose (*SD*)	Attrition
Topiramate versus PLB	Jankovic et al. (2010)	Parallel RCT	29	16.5 (9.9); 7–65	6	100% TS (34% ADHD, NR% OCD)	118 mg/day (NR)	67% completed 93% analysed
Antiparkinsonian agents								
Selegiline versus PLB	Feigin et al. (1996)	Cross-over RCT	24	12 (2.5); 7–16	8	100% TS (100% ADHD, NR% OCD)	10 mg/day (NR)	63% completed % analysed NR
Antipsychotics								
Aripiprazole versus PLB	Yoo et al. (2013)	Parallel RCT	61	11.0 (2.75); 6–18	10	100% TS (10% ADHD, 5% ODD)	11.0 mg/day (6.1)	89% completed 98% analysed
Haloperidol versus PLB	Sallee, Nesbitt, Jackson, Sine, and Sethuraman (1997)	Cross-over RCT	22	10.2 (2.5); 7–16	6	100% TS (59% ADHD, 23% OCD)	3.5 mg/day (2.2)	95% completed 100% analysed
Pimozide versus PLB	Sallee et al. (1997)	Cross-over RCT	22	10.2 (2.5); 7–16	6	100% TS (59% ADHD, 23% OCD)	3.4 mg/day (1.6)	95% completed 100% analysed
Risperidone versus PLB	Scahill, Leckman, Schultz, Katsovich, and Peterson (2003)	Parallel RCT	26	11.1 (2.2); 6–18	8	100% TS (42% ADHD, 15% OCD)	2.5 mg/day (0.85)	92% completed 100% analysed
Ziprasidone versus PLB	Sallee et al. (2000)	Parallel RCT	28	11.6 (NR); 7–16	8	97% TS 3% CTD (54% ADHD, 36% OCD)	28.2 mg/day (9.6)	86% completed 96% analysed
CNS stimulants								
Methylphenidate versus PLB	Kurlan et al. (2002)	Parallel RCT	136	10.2 (1.9); 7–14	16	94% TS 6% CTD (100% ADHD, 16% OCD)	25.7 mg/day (NR)	89% completed 100% analysed
Methylphenidate versus PLB	Gadow, Nolan, and Sverd (1992)	Cross-over RCT	11	8.3 (1.96); 6–11	2	91% TS 9% CTD (100% ADHD, NR% OCD)	0.5 mg/kg/day (NR)	NR
Methylphenidate versus PLB	Gadow, Sverd, Nolan, Sprafkin, and Schneider (2007)	Cross-over RCT	71	9.0 (1.4); 6–12	2	96% TS 4% CTD (100% ADHD, 4% OCD)	14.3 mg/day (3.3)	NR
Dopamine agents								
Pergolide versus PLB	Gilbert, Sethuraman, Sine, Peters, and Sallee (2000)	Cross-over RCT	24	NR; 7–17	6	100% TS or CTD (68% ADHD, 32% OCD)	0.20 mg/day (NR)	79% completed 79% analysed
Pergolide versus PLB	Gilbert et al. (2003)	Parallel RCT	57	10.7 (2.4); 7–17	8	100% TS or CTD (24% ADHD, 19% OCD)	0.43 mg/day (NR)	84% completed 89% analysed
Pramipexole versus PLB	Kurlan et al. (2012)	Parallel RCT	63	NR; 6–17	6	100% TS (NR% ADHD and OCD)	0.50 mg/day (NR)	NR
Muscle relaxants								
Baclofen versus PLB	Singer, Wendlandt, Krieger, and Giuliano (2001)	Cross-over RCT	10	11.7 (2.0); 8–14	4	100% TS (50% ADHD, 30% OCD)	60 mg/day (NR)	90% completed 90% analysed
Smoking cessation agents								
Nicotine patch + AP versus PLB patch + AP	Silver, Shytle, Philipp, et al. (2001)	Parallel RCT	70	11.1 (2.0); 8–17	5	100% TS (NR% ADHD and OCD)	7 mg/day + HAL 1.63 ng/ml (NR)	80% completed 80% analysed

Table 2 (continued)

Treatments	Study	Design	*N*	Age: mean (*SD*); range	Duration (weeks)	Diagnosis (comorbid diagnosis)	Mean dose (*SD*)	Attrition
Nicotine patch + AP versus PLB patch + AP	Howson et al. (2004)	Cross-over RCT	23	11.9 (2.9); 8–17	1	100% TS (86% ADHD 32% OCD)	7 mg/week + AP (NR)	61% completed 61% analysed
Selective norepinephrine reuptake inhibitor								
Atomoxetine versus PLB	Allen et al. (2005)	Parallel RCT	148	11.2 (2.5); 7–17	18	79% TS 21% CTD (100% ADHD, 3% OCD)	1.33 mg/kg/day (0.22)	70% completed 98% analysed
Dietary interventions								
Omega 3 fatty acids versus PLB (olive oil)	Gabbay et al. (2012)	Parallel RCT	33	11.3 (3.0); 6–18	20	100% TS (61% ADHD, 55% OCD)	4074 mg/day (NR)	76% completed 100% analysed

NR, not reported; ADHD, attention-deficit hyperactivity disorder; AP, antipsychotic drug; CTD, chronic tic disorder; HAL, haloperidol; NR, not reported; PLB, placebo; OCD, obsessive compulsive disorder; RCT, randomised controlled trial; TS, Tourette syndrome.
[a]Nine (23%) participants (five in the placebo and four in the clonidine treatment groups) were 18 years or older.

Discussion

Habit reversal training (HRT) and ERP are recommended as first-line interventions for children and young people with TS or CTD (Verdellen et al., 2011). Our results broadly support this recommendation, with evidence that behavioural interventions (CBIT/HRT) have a similar magnitude of effect to pharmacological interventions and the profile of adverse effects is more favourable. However, for many young people with tics and Tourette syndrome, pharmacological treatments may be considered either because of the limited availability and access to behavioural interventions, or lack of treatment response. Despite the widespread use of antipsychotic medications for the treatment of tics, certainty in the effect estimates (quality of the body of evidence) was low for their overall efficacy in children and young people. Given that it is well established that the side-effect profiles differ between antipsychotic drugs, we considered the antipsychotics individually. The evidence for risperidone came from one small study and, although this study was determined to have a low risk of bias, the true magnitude of effect is uncertain. For pimozide and haloperidol, evidence was from the same small cross-over study with uncertain validity, and similarly, for ziprasidone, only a single small study with uncertain validity contributed evidence. Aripiprazole compared favourably to placebo in our review and in head-to-head comparisons with other antipsychotics (haloperidol and tiapride) (Liu et al., 2011; Yoo et al., 2011). Against placebo, there was no increased risk of adverse events, including extrapyramidal symptoms, but the trial (Yoo et al., 2013) included only 60 participants in the safety evaluation and therefore may not have sufficient statistical power to detect treatment-related adverse effects. These findings suggest that aripiprazole may be a useful antipsychotic agent for the treatment of tics, with a similar magnitude of effect to that of other antipsychotic agents. Olanzapine has only been assessed in a head-to-head study (vs. haloperidol) (Ji, Li, Li, & Guo, 2005), that provided low-quality evidence for its comparative efficacy. In light of the current low-quality evidence of efficacy and potential for adverse effects, there appears to be a need for further research into the use of antipsychotics for children and young people with TS.

The review found moderate certainty in the estimate of effect for the use of the α2-adrenergic receptor agonists clonidine and guanfacine (based on four studies with low risk of bias). When the results were pooled, there was a medium-sized benefit (SMD = −0.74). We took an a priori decision to separate trials of oral clonidine from patches because the group felt there was a high risk of heterogeneity between trials of oral clonidine and patches. A post hoc analysis combining these trials continued to demonstrate benefit (SMD = −0.54) but statistical heterogeneity was high and unlikely to be

Table 3 Characteristics of included trials assessing behavioural and physical interventions for Tourette syndrome

Treatments	Study	Design	*N*	Age: mean (*SD*); range	Duration (weeks)	Diagnosis (comorbid diagnosis); medication	No. of sessions or dose	Attrition
Behavioural interventions								
Anger control training versus TAU	Sukhodolsky et al. (2009)	Parallel RCT	26	12.7 (0.88); 11–16	10	100% TS or CTD (69% ADHD, 35% OCD); 69% on medication	10	100% completed 100% analysed
HRT versus waitlist	Azrin and Peterson (1990)	Parallel RCT	7	11.9 (3.5); 6–16	13	100% TS (NR% ADHD/OCD); 43% on medication	7	64% completed[a] 64% analysed
CBIT versus supportive psychotherapy	Piacentini et al. (2010)	Parallel RCT	126	11.7 (2.3); 9–17	10	94% TS, 6% CTD (26% ADHD, 19% OCD); 37% on medication	8	90% completed 100% analysed
Parent training versus TAU	Scahill et al. (2006)	Parallel RCT	23	8.9 (2.0); 6–12	10	75% TS, 25% CTD (42% ADHD, 17% OCD); 83% on medication	10	96% completed 96% analysed
Relaxation training versus minimal therapy	Bergin, Waranch, Brown, Carson, and Singer (1998)	Parallel RCT	16	11.3 (3.0); 7–18	6	100% TS (57% ADHD, 0% OCD); 13% on medication	6	70% completed 70% analysed
Physical interventions								
Botulinum toxin versus PLB	Marras et al. (2001)	Cross-over RCT	18	Median 31.5; 15–55	2	78% TS, 22% CTD (NR% ADHD/OCD); 44% on medication	Single variable dose injection	90% completed 90% analysed
IV immunoglobulin versus PLB	Hoekstra et al. (2004)	Parallel RCT	29	29.8 (NR); 14–63	14	90% TS, 10% CTD (NR% ADHD/OCD); 55% on medication	1 g/kg/day on 2 days	97% completed 97% analysed

ADHD, attention-deficit hyperactivity disorder; CTD, chronic tic disorder; IV, intravenous; NR, not reported; PLB, placebo; OCD, obsessive compulsive disorder; RCT, randomised controlled trial; TAU, treatment as usual; TS, Tourette syndrome.

[a]Four patients dropped out of the whole study (composed of adults and children). Attrition based on conservative assumption that all the participants who dropped out were children.

Table 4 Results of trials assessing interventions for Tourette syndrome

Intervention	Study	Age	Benefit (effect size and 95% CI)	Overall adverse effects (AEs) or serious AEs (effect size and 95% CI)[a]	Certainty in the effect estimate for benefit (GRADE)[b]
α2-adrenergic receptor agonists					
Clonidine or guanfacine	Cummings et al. (2002) Kurlan et al. (2002) Leckman et al. (1991) Scahill et al. (2001)	CYP CYP Mixed CYP	Tics/global score (k = 4): SMD = −0.74 (−1.06, −0.42)	Clonidine AE (k = 1): RR = 1.87 (1.24, 2.81) Guanfacine AE (k = 2): No differences between groups reported	Moderate[c]
Clonidine patch	Du et al. (2008) Zhong et al. (2007)	CYP CYP	Tics (k = 1): SMD = −0.10 (−0.32, 0.12)	AE (k = 1): RR = 0.34 (0.13, 0.89)	Moderate[d]
Antihypertensives					
Mecamylamine	Silver, Shytle, Sheehan et al. (2001)	CYP	Tics (k = 1): Comparative effect NR	–	Low[c,d]
Antidepressants (SSRI)					
Fluoxetine	Kurlan et al. (2002)	CYP	Motor tics (k = 1): SMD = −0.90 (−2.15, 0.34)	–	Very low[c,d]
Antidepressants (TCA)					
Desipramine	Singer et al. (1995) Spencer et al. (2002)	CYP CYP	Tics (k = 1): SMD = −0.96 (−1.63, −0.29)	AE (k = 1): RR = 1.73 (1.14, 2.64)	Low[c]
Antiemetics					
Metoclopramide	Nicolson et al. (2005)	CYP	Tics (k = 1): SMD = −1.43 (−2.28, −0.59)	–	Low[c,d]
Ondansetron	Toran et al. (2005)	CYP	Tics (k = 1): SMD = −0.38 (−1.42, 0.66)	–	Very low[c,d]
Anticonvulsants					
Levetiracetam	Smith-Hicks et al. (2007)	CYP	Tics (k = 1): SMD = −0.23 (−0.85, 0.39)	–	Low[c,d]
Topiramate	Jankovic et al. (2010)	Mixed	Tics (k = 1): SMD = −0.88 (−1.68, −0.08)	AE: RR = 0.79 (0.56, 1.11)	Low[c]
Antiparkinsonian agents					
Selegiline	Feigin et al. (1996)	CYP	Global (k = 1): SMD = −0.72 (−1.45, 0.02)	–	Low[c,d]
Antipsychotics					
Any	Sallee et al. (1997) Sallee et al. (2000) Scahill et al. (2003) Yoo et al. (2013)	CYP	Tics (k = 4): SMD = −0.78 (−1.13, −0.43)	–	Low[c,d]
Aripiprazole	Yoo et al. (2013)	CYP	Tics (k = 1): SMD = −0.62 (−1.14, −0.11)	AE: RR = 1.05 (0.77, 1.43) EPS: SMD = 0.28 (−0.24, 0.79)	Moderate[c]
Haloperidol	Sallee et al. (1997)	CYP	Tics (k = 1): SMD = −0.50 (−0.89, −0.10)	EPS: SMD = 0.51 (0.11, 0.90)	Low[c,d]
Pimozide	Sallee et al. (1997)	CYP	Tics (k = 1): SMD = −0.81 (−1.24, −0.38)	EPS: SMD = 0.20 (−0.18, 0.58)	Low[c,d]
Risperidone	Scahill et al. (2003)	CYP	Tics (k = 1): SMD = −1.18 (−2.02, −0.34)	–	Low[c]
Ziprasidone	Sallee et al. (2000)	CYP	Tics (k = 1): SMD = −0.78 (−1.54, 0.06)	AE: RR = 1.68 (1.05, 2.70)	Low[c,d]
CNS stimulants					
Methylphenidate	Gadow et al. (1992) Gadow et al. (2007) Kurlan et al. (2002)	CYP CYP CYP	Motor tics (k = 3): SMD = −0.03 (−0.20, 0.15)	–	Low[c,d]
Dopamine agents					
Pergolide	Gilbert et al. (2000) Gilbert et al. (2003)	CYP CYP	Tics (k = 1): SMD = −0.59 (−1.21, 0.02)	AE (k = 2): SMD = −0.05 (−0.49, 0.38) QT interval (k = 1): MD 13.50 (−4.29, 31.29)	Low[c]
Pramipexole	Kurlan et al. (2012)	CYP	Tics (k = 1): SMD = −0.00 (−0.53, 0.53)	AE: RR = 1.62 (0.70, 3.76)	Low[c,d]

Table 4 (continued)

Intervention	Study	Age	Benefit (effect size and 95% CI)	Overall adverse effects (AEs) or serious AEs (effect size and 95% CI)[a]	Certainty in the effect estimate for benefit (GRADE)[b]
Muscle relaxants					
Baclofen	Singer et al. (2001)	CYP	Tics (k = 1): SMD = −0.54 (−1.50, 0.42)	–	Very low[c,d]
Smoking cessation agents					
Nicotine patch	Howson et al. (2004)	CYP	Motor tic score (k = 2): SMD = −0.03 (−0.49, 0.43)	–	Low[c,d]
	Silver, Shytle, Philipp, et al. (2001)	CYP			
Selective norepinephrine reuptake inhibitor					
Atomoxetine	Allen et al. (2005)	CYP	Tics (k = 1): SMD = −0.32 (−0.65, 0.01)	–	Moderate[c]
Dietary interventions					
Omega 3 fatty acids	Gabbay et al. (2012)	CYP	Tics (k = 1): SMD = −0.24 (−0.93, 0.45)	AE: 'no significant treatment differences' were reported	Low[c,d]
Behavioural interventions					
Anger control training	Sukhodolsky et al. (2009)	CYP	Tics (k = 1): SMD = −0.58 (−1.37, 0.20)	–	Low[c,d]
HRT/CBIT	Azrin and Peterson (1990)	CYP	Tics (k = 2): SMD = −0.64 (−0.99, −0.29)	–	Moderate[c]
	Piacentini et al. (2010)	CYP			
Parent training	Scahill et al. (2006)	CYP	Tics (k = 1): SMD = 0.29 (−0.53, 1.12)	–	Very low[c,d]
Relaxation training	Bergin et al. (1998)	CYP	Global (k = 1): SMD = −0.61 (−1.76, 0.54)	–	Very low[c,d]
Physical interventions					
Botulinum toxin	Marras et al. (2001)	Mixed	Tics (k = 1): SMD = 0.02 (−0.63, 0.67)	–	Low[c,d]
IV immunoglobulin	Hoekstra et al. (2004)	Mixed	Tics (k = 1): SMD = −0.51 (−1.25, 0.23)	AE: RR = 3.48 (1.49, 8.16)	Low[c,d]

AE, adverse event; CYP, children and young people; EPS, extrapyramidal symptoms; k, number of studies; Mixed, mixed sample of CYP and adults; RR, relative risk; TS, Tourette syndrome; SMD, standardised mean difference.
[a]Specific adverse events, other than those considered to be serious, are not reported here.
[b]Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence are as follows. High = further research is very unlikely to change our certainty in the effect estimate; moderate = further research is likely to have an important impact on our certainty in the effect estimate and may change the estimate; low = further research is very likely to have an important impact on our certainty in the effect estimate and is likely to change the estimate; and very low = we are very uncertain about the estimate.
[c]Sample size does not reach optimal information size (outcome downgraded by one or two levels).
[d]Overall, studies reporting this outcome were associated with high risk of bias (outcome downgraded by one or two levels).

due to chance, making the pooled estimate difficult to interpret. We found that clonidine was associated with increased rates of sedation, but for guanfacine, no increased rates of side effects were reported. Alpha 2-adrenergic receptor agonists appear to be useful for the treatment of children with tic disorders. Given their efficacy and relatively benign adverse effect profile, these agents may be a good first-line pharmacological treatment for tics in children and young people. A pilot study (double-blind RCT) is currently being conducted to determine the efficacy and safety of extended-release guanfacine in children with tic disorders (NCT01547000) and may provide further evidence for the efficacy and safety of this drug. Guanfacine, previously licensed in the United States is now being reviewed for licensing (marketing authorisation) in the United Kingdom (European Union). In our review, an important finding for clinical practice was that stimulants used to treat comorbid ADHD and TS/tics did not appear to worsen tics. This finding supports other recent systematic reviews and meta-analyses which have found no increased risk of new onset tics, or tic worsening with stimulant medication compared to placebo (Cohen et al., 2015; Pringsheim & Steeves, 2011). However, despite there being no overall group effect of stimulants on tics, clinical reports indicate that tics may be exacerbated in certain individuals at higher stimulant doses, with tic worsening reversible by stimulant dose reduction (Castellanos, 1997).

There was no controlled evidence for the use of DBS or repetitive transcranial magnetic stimulation (rTMS) in children. These physical treatments are

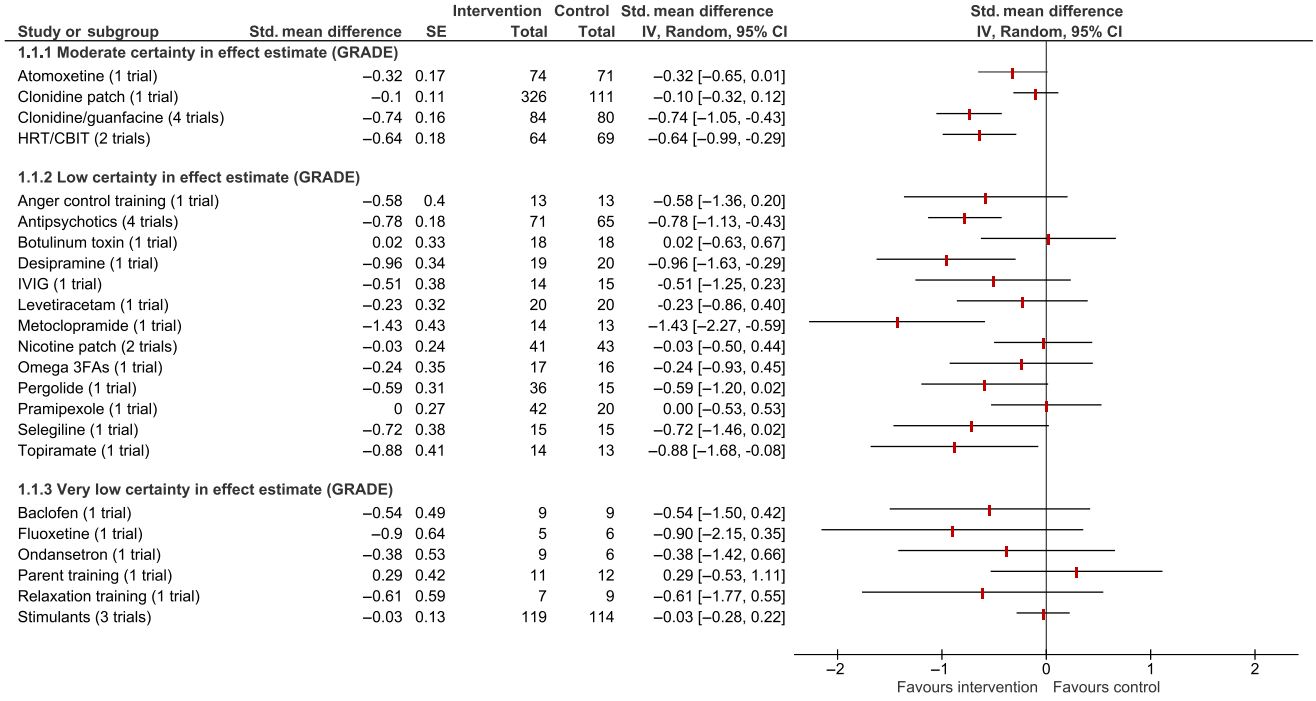

Figure 2 Effect sizes for interventions in children and young people with Tourette syndrome categorised by GRADE assessment (CBIT, comprehensive behavioural intervention for tics; HRT, habit reversal training; IVIG, intravenous immunoglobulin)

currently experimental (rTMS) or confined to use in adults (DBS). Given the current lack of evidence of efficacy and the safety risks involved, treatment of paediatric populations appears inappropriate.

The review highlighted the lack of evidence for alternative treatments that are in current use. Evidence from studies of botulinum toxin and omega-3 fatty acids was graded as low quality. The only trial of acupuncture in children with TS or CTD was a head-to-head study against haloperidol (Xu, Ze, Shu-zi, Da-Peng, & Yuan-zheng, 2003) and provided very low-quality evidence. There was no evidence for the use of dietary supplements, vitamins, yoga or chiropody.

It should be noted that efficacy of behavioural therapy was largely driven by the trial of CBIT (Piacentini et al., 2010), which had a much bigger sample size and slightly larger effect size (SMD = −0.64, 95% CI −1.0, −0.29) than the trial of HRT (Azrin & Peterson, 1990). Nevertheless, despite evidence for the efficacy of behavioural therapy and low risk of associated adverse events, difficulties around access and financial constraints may hinder the widespread use of behavioural treatments. There was some indication that therapy was effective with a reduced number of treatment sessions (after 5 sessions, SMD = −0.48, 95% CI −0.83, −0.12) (Piacentini et al., 2010) but the longer term benefits of differing treatment lengths are unclear. A small study comparing CBIT delivered via video conference compared to face-to-face therapy has shown promise that this may be a useful alternative mode of delivery for increasing availability of behavioural therapy (Himle et al., 2012), but further research would be needed to indicate whether this is an effective alternative to face-to-face delivery. In studies of behavioural therapy, patients receiving medication for tics were included and so questions remain around the relative benefits of behavioural treatments alone and in combination with medications. Further research comparing behavioural therapy with or without medication together with an analysis of the moderating effects of tic severity and comorbid conditions would contribute important information to inform treatment practice.

The main limitation of this review was the paucity of available evidence and, to an extent, the review strategy. The small number and sample size of studies for any given intervention limited their interpretation and there is still uncertainty around which treatments are best and the magnitude of their effects. Many interventions had no, or only very low quality, evidence and no conclusions can be drawn about their efficacy. The majority of studies compared short-term post-treatment effects, and the longer term efficacy of interventions is uncertain. Most studies did not report changes in comorbid conditions and focussed on changes in tics and there is also uncertainty around the effect of interventions on comorbid symptoms and TS-related impairments. There is a need to formally evaluate the impact of psychoeducation, as this typically incorporates information on tics and comorbidities, and helps families and clinicians establish where the most significant impairment lies. The clinical significance of changes in tic scores, that is, the minimum clinically important difference (MCID) on commonly used scale such as the YGTSS requires further study

and should be established a priori in future treatment trials. Several studies have shown that although tics may represent the most evident symptom, the major impairment lies with one or more psychiatric comorbidities (Bernard et al., 2009; Gorman et al., 2010). Treatment choices may differ depending on the relative balance of impairment associated with tics and comorbid symptoms, but the evidence base for the treatment of comorbidities with TS and CTD lies outside the scope of this review. This is a limitation, as in clinical practice a priority for improving function may be detection and treatment of comorbidity. Rates of psychiatric comorbidity are high in Tourette syndrome, and emerge early in life, a recent large study reporting a life-time prevalence of 86% (Hirschtritt et al., 2015). For example, the presence of a significant anxiety disorder may contribute markedly to social and educational impairment in a child, although tics may be the presenting difficulty. This clinical formulation needs to be discussed with the family, and the relative impact of symptoms examined. It may be that in an individual clinical situation, a first treatment step would be a trial of anxiety treatment, which might in itself lead to reduction in tics, or better tolerance of the same level of tics. These concepts of hierarchical/step-wise treatments are familiar to clinicians working with children with mixed neurodevelopmental disorders, and further research is needed to explore the effects of the treatment of psychiatric comorbidity on tic severity and impact. An innovative trial design called Sequential, Multiple Assignment, Randomized Trial (SMART), which is used for development of personalised treatments (Collins, Nahum-Shani, & Almirall, 2014) may be particularly appropriate for the evaluation of step-wise treatment approaches for tics and Tourette syndrome. Finally, studies reviewed indicated a high degree of interindividual variability in response, indicating that, in practice, it may be difficult to predict which treatment an individual will respond to best.

The long-term side effects associated with interventions, particularly with pharmacological treatments, are unclear. This review only synthesised short-term controlled studies and only considered safety outcomes in studies of TS or CTD patients. A review of use across other disorders in children and young people including longer term uncontrolled studies would give a much more comprehensive assessment of the evidence for adverse effects but this was outside the scope of the review. However, many of the important side effects were identified by our work and, by restricting the review to controlled studies, we could obtain more reliable estimates of the proportion of patients likely to have experienced adverse events. Another limitation introduced by the restriction to placebo-controlled studies was that interventions investigated with other study designs were not assessed in the review. However, the poor quality of evidence provided by uncontrolled studies limits their interpretation and they were unlikely to have added value to the review.

Despite these limitations, the present systematic review has provided a strong foundation to build on, including registration of the review protocol, robust methods for identifying the evidence, an assessment of risk of bias and application of the GRADE approach to rating certainty in the estimates of effect. Nevertheless, considering the small amount of available evidence, continued research and review of the evidence for all types of treatments is needed, in particular, the combination of pharmacological and behavioural interventions and the use of technology to increase access to behavioural interventions.

Conclusion

In summary, the balance of clinical benefits to harm favours α2-adrenergic receptor agonists (e.g. clonidine, guanfacine) as first-line drug treatments for tics in children and young people. Antipsychotics (e.g. risperidone, aripiprazole) may be as effective as α2-adrenergic receptor agonists but considering the low quality of evidence and adverse effect profile, they may be reserved for treatment of tics when α2-adrenergic receptor agonists are either ineffective or poorly tolerated. There is evidence that HRT/CBIT is an effective treatment for tics in children and young people with TS. However, there is currently no evidence available regarding the relative benefits of HRT/CBIT alone compared to combining medication and HRT/CBIT. In clinical practice, young people and their parents may prefer to start a behavioural intervention before considering medication (Cuenca et al., 2015). Given the broadly similar efficacy of behavioural and pharmacological interventions it would seem reasonable to give significant weighting to these patient preferences. However, it should be remembered that we know very little about the relative efficacy of behavioural interventions alone or in combination with medication. Importantly, our review showed that stimulant medication used to treat comorbid ADHD/TS does not appear to exacerbate tics. There is currently no evidence to suggest that the physical/alternative interventions reviewed (DBS, rTMS, botulinum toxin, IV immunoglobulins, omega 3 fatty acids and acupuncture) are sufficiently effective and safe to be considered as treatments for tics in children and young people with TS. Given that young people and their parents may seek alternative treatments, it is important to emphasise that their use is not supported by any robust evidence.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Databases searched.
Appendix S2. Search strategy for Embase, Medline, PreMedline, PsycINFO (searched via OVID).

Acknowledgements

M.P. conducted the systematic review including the acquisition of data and data analysis and drafted parts of the manuscript. T.K. and C.G. made substantial contributions to the conception and design of the project, contributed to interpretation of the data and critically revised the manuscript. C.W. developed the systematic review protocol, oversaw the review work, contributed to the analysis and interpretation of data and drafted parts of, and critically revised, the manuscript. P.T., M.G., T.H., I.H., G.J., T.M., H.R., M.R. and J.S. were involved in the conception and design of the project, contributed to the interpretation of data and commented on the manuscript. C.H. was the principal investigator and made substantial contributions to the conception and design of project, interpretation of data and drafted parts of, and critically revised, the manuscript.

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Key points

Key practitioner message

- Tourette syndrome (TS) and chronic tic disorder affect 1%–2% of children and young people and cause significant psychosocial impairment. However, there is a lack of evidence-based clinical guidance for practitioners.
- Behavioural intervention for tics (HRT/CBIT) demonstrates similar effectiveness to medication, and a more favourable adverse effect profile, which suggests that it should be offered as a first-line intervention for young people with tics.
- When medication is considered appropriate, the balance of clinical benefits to harm may favour α 2 agonists (i.e. clonidine and guanfacine).
- Antipsychotics are likely to be useful but may be reserved for when noradrenergic agents are either ineffective or poorly tolerated.
- Stimulant medication used to treat comorbid ADHD/TS does not appear to exacerbate tics. However, if tic worsening does occur it is more likely with higher doses and reversible with stimulant dose reduction.
- There is currently no evidence regarding the relative benefits of HRT/CBIT alone compared to benefits of combining medication and behavioural intervention.
- There is currently no evidence to suggest that the physical/alternative interventions reviewed are sufficiently effective and safe to be considered as treatments for tics in children and young people with TS.

Areas for future research

- Future research should focus on the development and evaluation of digital technologies that can increase access to behavioural interventions.
- The cost-effectiveness of different treatment interventions for tics needs to be assessed.
- RCTs assessing the relative benefits of HRT/CBIT alone compared to combining medication and HRT/CBIT are needed.
- Innovative trial designs such as Sequential, Multiple Assignment, Randomized Trial (SMART) may be particularly appropriate for the evaluation of step-wise treatment approaches for tics and Tourette syndrome.
- The safety and efficacy of the physical/alternative interventions reviewed (DBS, rTMS, botulinum toxin, IV immunoglobulins, omega 3 fatty acids and acupuncture) also need to be assessed.
- The moderating effects of age, tic severity, premonitory urges and common comorbidities (e.g. ADHD, OCD, anxiety and depression) on treatment of tics needs to be assessed.
- The moderating effects of tics on treatment outcomes for common comorbid conditions (e.g. ADHD, OCD, anxiety and depression) needs to be assessed.

Note

1. Eligible if they were licensed for use in any disorder in North America, Europe or Australasia.

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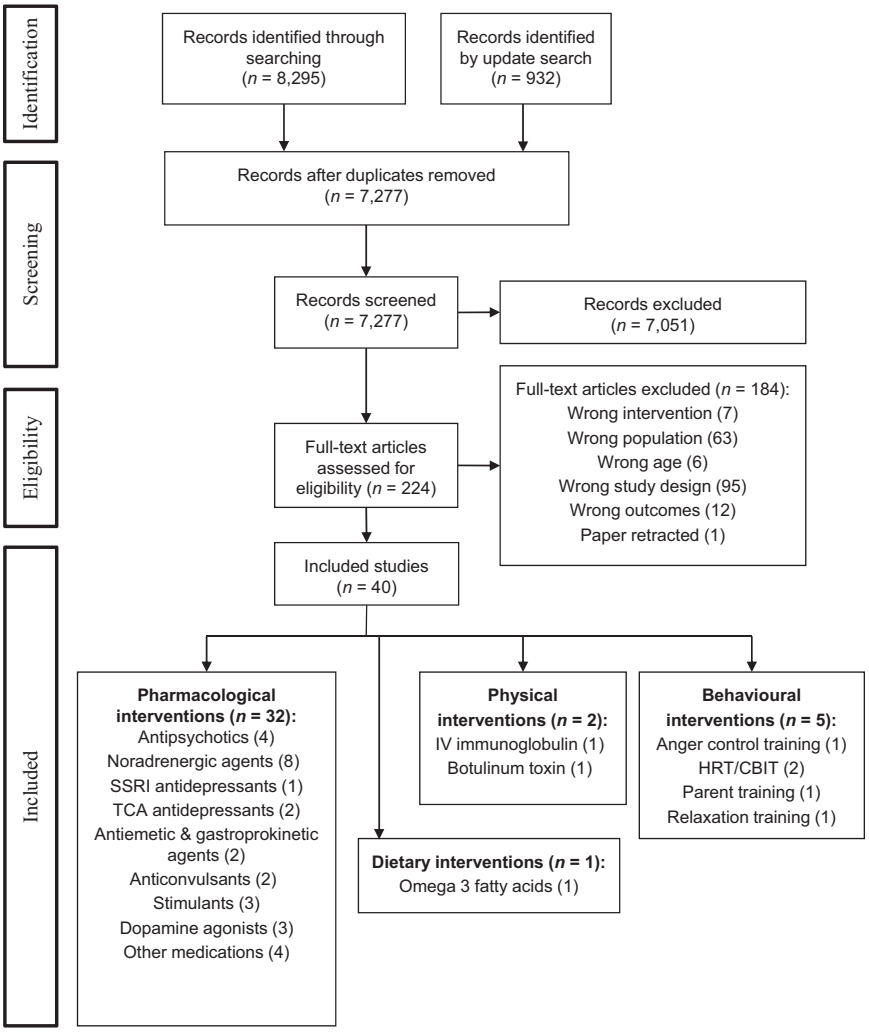

Tourette syndrome (TS) is a common neurodevelopmental condition affecting approximately 1% of children and young people (c. 70,000 people age 7–17 years in England) which if untreated has a major adverse impact on mental health, social functioning and quality of life. Despite the prevalence of TS in young people being greater than diabetes and epilepsy, it remains a frequently misunderstood condition and its seriousness at a population level is typically overlooked, as evidenced by the absence of evidence-based clinical guidelines. TS is characterised by persistent and impairing motor and vocal tics which typically emerge in childhood, run a waxing and waning course and carry on into adult life in about 30% of young people. Tics can be highly stigmatising, especially for teenagers, and often lead to bullying, peer victimisation, social exclusion, depression and self-harm. TS is associated and frequently coexists with other neurodevelopmental and mental health conditions including ADHD (60%), anxiety disorder (40%), OCD (30%) and ASD (20%) which add to the complexity of clinical management. Evidence from this major systematic review and meta-analysis shows that clinically effective treatments for tics in children and young people exist and include medication (e.g. α2-noradrenergic agonists and antipsychotics) and behavioural interventions, including exposure and response prevention, habit reversal training (HRT) and the comprehensive behavioural intervention for tics programme which combines psychoeducation with HRT. The results of this review suggest that both medication and behavioural interventions have similar efficacy (moderate effect size) in treating tics, with behavioural interventions having a more favourable adverse effect profile. When considering medication, the more favourable adverse effect profile of α2-noradrenergic agonists suggests that these agents should be offered before antipsychotics. However, psychoeducation and behavioural interventions are generally the preferred treatment option, particularly as first-line interventions, by young people and their parents. Despite demonstrated efficacy, access in most healthcare systems to evidence-based behavioural interventions for tics is extremely poor. Therefore, given the healthcare challenge of delivering behavioural interventions at scale with existing numbers of therapists and the traditional model of face-to-face delivery there is a pressing need to develop and evaluate digitally delivered interventions for young people with tics using a stepped-care model of therapist support.