

Therapist-supported online remote behavioural intervention for tics (ORBIT) in children and adolescents: A single-blind randomised controlled trial

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SUMMARY (300 word limit)

Background: Behaviour therapy is an effective treatment in children and adolescents with tic disorders but is rarely available. Online delivery could widen access to therapy. We evaluated the efficacy of internet-delivered, therapist-supported and parent-assisted Exposure and Response Prevention (ERP) for tics.

Methods: Multi-centre, parallel group, single-blind, randomised controlled trial. Eligible participants were aged 9-17 years with Tourette syndrome/chronic tic disorder, who had not received behaviour therapy for tics within 12 months, and had a Yale Global Tic Severity Scale (YGTSS) Total Tic Severity Score (TTSS) of >15, or >10 if motor or vocal tics only. Participants were recruited via 16 patient identification centres, two study sites, or online self-referral, and were randomised (1:1) by blinded outcome-assessors to receive either 10 weeks of ERP or psychoeducation (active control). The primary outcome was YGTSS-TTSS at 3 months' post-randomisation, analysis was by intention-to-treat. The mean cost per patient for the intervention and health care costs were calculated. Registrations are ISRCTN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

Findings: Between 8th May 2018 and 30th September 2019, 224 participants were enrolled; 112 to ERP and 112 to psychoeducation. The ERP intervention reduced YGTSS-TTSS by 2.29 points (95% CI: -3.86 to -0.71) compared to the psychoeducation group at 3 months, an effect that increased by 6 months post-randomisation (-2.64, 95% CI: -4.56 to -0.73). The average therapist time spent supporting the intervention was 2.5 hours. The additional cost per participant of the ERP intervention compared to psychoeducation was £159 (95% CI -£53

to £370). There were two unrelated serious adverse events, both in the psychoeducation group.

Interpretation: Online-delivered, therapist-supported ERP therapy is clinically effective at reducing tics, with minimal therapist contact time. Online delivery could improve access to evidence-based treatment for tics in children and adolescents.

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INTRODUCTION

Tic disorders such as Tourette syndrome (TS) or chronic tic disorder (CTD) are common conditions affecting up to 1% of young people.¹ Tics can lead to significant impairment and isolation² and often co-occur with other conditions. Although there are effective pharmacological treatments for tics, they are associated with side-effects such as weight-gain and cognitive dulling.^{2,3} Behavioural therapy (BT) demonstrates similar efficacy to pharmacotherapy for tics,^{1,3} with minimal adverse effects, and is recommended as first-line therapy.³

Effective behavioural therapies for tics include: Habit Reversal Training (HRT), where patients learn to detect tics and use a competing response (an incompatible action) to control them; Comprehensive Behavioural Intervention for Tics (CBIT) which combines HRT with relaxation, functional analysis and social support and Exposure and Response Prevention (ERP), where patients learn to tolerate the premonitory urge to tic and resist expressing it. In a head-to-head comparison, no difference was found in efficacy between ERP and HRT in reducing tic symptoms.⁴ A pivotal study demonstrated superior tic reduction and clinical improvement for children who received eight sessions of CBIT compared to supportive therapy with tic psychoeducation.⁵

However, behavioural therapy for tics is rarely available. In the United Kingdom (UK), only one in five children and adolescents with tic disorders has access, with less than half of them receiving the recommended number of sessions.⁶ Barriers include a shortage of trained therapists, and therapy only being offered at specialist treatment centres meaning patients often have to travel long distances. The COVID-19 pandemic has further highlighted the urgent need to offer cost-effective interventions that can be delivered remotely in digital formats.⁷

Across different mental health conditions, meta-analyses demonstrate that online internet-delivered cognitive behavioural therapy (iCBT) is as efficacious as face-to-face delivery and can result in substantial cost-savings.⁸ Evidence from studies of internet-delivered, cognitive behavioural therapy (iCBT) with adults suggests that therapist-guided interventions lead to better outcomes⁹ than standalone iCBT. Given the lack of specialist child therapists in this area, a blended approach whereby the core therapeutic content is delivered online in a standardised chapter format, but is supported asynchronously by a non-specialist therapist, whose primary role is to promote engagement may offer a more pragmatic solution. A meta-analysis of CBT for anxiety and depression in children argued that parents are also a potentially valuable but under researched resource to support the delivery of iCBT in children.¹⁰

Recent research in Sweden has developed an online platform to deliver therapist-supported iCBT called “BIP” (*Barninternetprojektet* [Child Internet Project]; <http://www.bup.se/bip>). The platform has been used to deliver therapy to children with a range of mental health conditions, including anxiety, and obsessive-compulsive disorder.^{11,12} Compared to other conditions, internet delivery of therapy for tics has received less interest.¹³ One small pilot study using the BIP platform compared 10 weeks of therapist-guided, parent-supported HRT against ERP in children and adolescents with tics who were followed-up at 3 and 12 months

post-treatment. The findings indicated that the method of delivery was highly acceptable to families. Whilst both therapeutic groups demonstrated a reduction in tic severity and impairment and improved quality of life, only the group who received ERP experienced a significant reduction in tic severity.¹⁴ Although this pilot study was not designed or powered to evaluate efficacy, the results support the feasibility and promise of online ERP for treating tics and justify further investigation to assess clinical efficacy and cost-effectiveness. In the present study, we aimed to evaluate the clinical efficacy and costs of a therapist-supported, parent-assisted internet-delivered ERP programme for tics in children and adolescents in the UK.

METHODS

Study design

The Online Remote Behavioural Intervention for Tics (ORBIT) trial was a two-arm, superiority parallel group, single-blind, multi-centre randomised control trial (RCT). It commenced in October 2018 with an anticipated completion date of September 2021. The trial was conducted across two Child and Adolescent Mental Health Services (CAMHS) in England. Site one (Queen's Medical Centre, Nottingham) was based in a mid-sized city and was a regional centre for tic treatment. Site two (Great Ormond Street Hospital, London) was a large metropolitan national paediatric centre of excellence.

The trial had two phases: Phase 1, a per-protocol follow-up for 6 months post-randomisation and Phase 2, a naturalistic follow-up for 18 months post-randomisation. The findings from Phase 1 are presented here.

Ethical and Health Research Authority (HRA) approval was received from North West Greater Manchester Research Ethics Committee on 23 March 2018 (ref.:18/NW/0079). The

published trial protocol is available online¹⁵ and was approved by an independent trial steering committee (TSC) and data monitoring committee (DMC). Two substantial amendments were made and can be found in the appendix p1. The trial was prospectively registered with the ISRCTN (ISRCTN70758207) and ClinicalTrials.gov (NCT03483493).

Participants

Eligible participants were aged 9-17 years with a moderate/severe tic disorder (TS or CTD) defined as scores on the Yale Global Tic Severity Scale (YGTSS)¹⁶ Total Tic Severity Score (TTSS) of >15, or >10 if only motor or vocal tics were present in the last 7 days. All participants were required to have broadband and smart phone/regular desktop/laptop computer access and the capacity to provide informed, written consent. Participants aged under 16 years were required to have a parent/guardian consent.

Exclusion criterion were: engaged in structured behavioural intervention for tics (e.g., HRT/CBIT or ERP) within the preceding 12 months or about to start; changed (i.e. starting or stopping) medication for tics within the previous two months; alcohol/substance dependence, psychosis; suicidality or anorexia nervosa (assessed via the Development and Well Being Assessment - DAWBA),¹⁷ suspected moderate/severe intellectual disability (assessed via Child and Adolescent Intellectual Disability Screening (CAIDS-Q));¹⁸ immediate risk to self or others; parent/carer of child unable to speak or read/write English.

Participants were recruited either by referral from one of 16 participating CAMHS or community paediatric clinics in England and the two study sites or by self-referral via Tourettes Action (UK tic disorder charity) website or the study website. Researchers (outcome assessors) completed an initial telephone consultation to determine likely eligibility and parents/carers completed the online DAWBA. Potential participants deemed eligible after

this initial screen attended a baseline assessment at one of the two study sites where assessors conducted further eligibility assessments including the YGTSS and CAIDS-Q. Written informed consent was obtained from participants or their parents/carers prior to undertaking the baseline assessment.

Randomisation and masking

Participants were randomly allocated in a 1:1 ratio to receive either 10 weeks of online, remotely delivered, therapist-supported ERP for tics or therapist-supported education about tics, referred to as psychoeducation (the active control). Outcome assessors randomly assigned participants using a secure web-based randomisation system developed by Sealed Envelope (<https://www.sealedenvelope.com/>) and managed by Priment Clinical Trials Unit, following specified standard operating procedures. Randomisations were stratified by study site using block randomisation with varying block sizes. Therapists and an independent assessor who did not conduct outcome assessments were informed of the allocation via email. The independent assessor verified that each participant was assigned to their allocated intervention – no instances of incorrect allocation were observed. Outcome assessors, statisticians, health economists, the trial manager and chief investigator were blind to group allocation. Participants were not directly informed of their allocation but may have been able to determine allocation once treatment commenced. Participants were reminded about the importance of masking at each follow-up, however, four instances of breaks of allocation concealment were reported to the trial manager. In all instances the child disclosed information about their treatment to the outcome assessor at the end of the follow-up assessment. In these cases, subsequent follow-ups were conducted by an alternative, blinded assessor. All instances were reviewed by the independent TSC and DMC for monitoring.

Procedures

The treatments were delivered via the secure online Swedish “BIP” platform. Participants and their parent/carers created their log-in details at the baseline assessment and set a treatment start date within 1-week of randomisation. Where possible, participants were briefly introduced to their therapist in person at the baseline assessment. The therapists assigned the participant to their allocated treatment and emailed a reminder to log in on their start date.

The treatment content has been described elsewhere,¹⁵ In summary, information was presented in chapters, which the family (child/adolescent and parent/carer) were requested to work-through. The therapist aimed to have 10-20 minutes contact time with the participants (combined contact time with the parent/carer and/or child/adolescent) each week to check progress, encourage motivation and answer questions, but did not deliver therapeutic content. Both the ERP intervention and the psychoeducation consisted of 10 chapters for the child/adolescent and 10 different chapters for parent/carers, designed to be delivered over 10 weeks. The therapist provided support for either ERP or psychoeducation through asynchronous contact (typically delivered via online messages sent through BIP) during these 10 weeks.

The internet-delivered ERP intervention was adapted from previously published treatment manuals by Verdellen et al.¹⁹ Participants were requested to first practice controlling all of their tics for increasingly long periods of time (response prevention), and then to deliberately provoke the premonitory urges whilst not releasing any tics (exposure and response prevention). Specific triggers to provoke the urge to tic were identified and used by participants, and then employed in everyday situations to improve generalizability of the gains. The psychoeducation comparator focussed on the history, prevalence and risk typically associated with tic disorders, and advised healthy habits, with no information on tic control.

For both interventions, the main treatment information was delivered via ten child-completed

chapters; participants were considered “treatment completers” if child chapters 1-4 were completed. The 10 parent chapters focused on how best to support the child during their treatment.

Therapists (graduate level education) were not required to have previous experience in treating tic disorders but were trained on the platform and its contents and received regular expert supervision. Further details can be found elsewhere.²⁰

Participants completed brief online measures mid-point through treatment (3 and 5 weeks) and completed online and outcome-assessor rated measures at baseline, 3, 6, 12 and 18 months post-randomisation. All follow-up outcome-assessor rated measures were completed remotely (via videoconferencing or telephone). Only the baseline appointment was conducted in person at one of the two study sites.

Outcomes

The primary outcome was tic severity at 3 months post-randomisation as measured by the YGTSS-TTSS. This is a semi-structured interview that combines separate scales of motor tics (score 0-25) and vocal tics (score 0-25), providing a total score 0-50, with higher scores indicating greater severity. It was completed by a blinded outcome-assessor. All outcome-assessors completed mandatory structured training on the YGTSS prior to starting and agreement with an expert rater was assessed every 6 months; full details can be found in appendix p2.

Secondary outcomes were obtained at baseline, 3 and 6 months post-randomisation, through interviews conducted by the blinded outcome assessors with the parent/carer and child/young person. They comprised: reduction in tic related impairment assessed through the YGTSS impairment scale (score 0-50); a global assessment of symptom improvement measured via the Clinical Global Impressions - Improvement scale (CGI-I),²¹ and global functioning

assessed via the Children's Global Assessment Scale (CGAS)²²; service use using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS) to include specific specialist tic disorder services and medications.²³

Parent/carers completed secondary outcomes online including measures of general behavioural and emotional difficulties (Strengths and Difficulties Questionnaire; SDQ);²⁴ generic health-related quality of life (proxy-rated child-health-utility-9D; CHU9D);²⁵ adverse events or side-effects (modified version of the Hill and Taylor²⁶ side-effects scale). A parent assessment of tics measured via the Parent Tic Questionnaire (PTQ)²⁷ was completed at these times and also at 5 weeks (mid-treatment).

Additional outcomes completed online by the child/adolescent included: generic quality of life (CHU9D) and a disease-specific measure of quality of life (Child and Adolescent Gilles de la Tourette Syndrome Quality of Life Scale; C&A-GTS-QOL).²⁸ Two additional measures were completed by the child/adolescent at 5 weeks (mid-treatment) as well as at baseline, 3 and 6 months, namely the Mood and Feelings Questionnaire (MFQ)²⁹ and the Spence Childhood Anxiety Scale (SCAS)³⁰. For the purpose of this study, a measure of treatment credibility was developed and completed online by parent/carers and child/adolescent at 3 weeks.¹⁵

Adverse events and side-effects were formally sought and recorded at each follow-up through the side-effects scale and MFQ. Participants were also encouraged to report them to their therapist or outcome assessor (see appendix p4-6).

Statistical analysis

Based on findings of other trials, the sample size was calculated in order to detect a clinically important average difference of 0.5 of a standard deviation between ERP and

psychoeducation with 90% power at $p < 0.05$ (two-sided). When allowing for 20% dropout, this required a total sample size of 220 participants.

Statistical analyses were conducted using Stata (version 16) in line with a predefined statistical analysis plan (SAP) approved by the TSC. Analysis was performed on an intention-to-treat basis, in which participants were analysed according to their allocated group. In line with the SAP, confidence intervals are reported rather than p-values.

Baseline demographic characteristics of participants, as well as their clinical and mental health outcomes at baseline and 3 and 6 months follow up, were summarised by randomised group using mean (standard deviation [SD]) or count (percentage) respectively for continuous and categorical data. The primary outcome was estimated using a linear regression model with YGTSS-TTSS at 3 months as the outcome and study group as the main explanatory variable, adjusting for YGTSS-TTSS at baseline and site (Nottingham/London).

Similar linear regression models were fitted to estimate the effect of the intervention on secondary outcomes at mid-treatment, 3 months and 6 months follow up (post-randomisation). The statistical model for the CGI-I did not adjust for baseline since this is a measure of change. Two unplanned subgroup analyses explored whether the effect of the intervention on the primary outcome was modified by either anxiety diagnosis or attention deficit hyperactivity disorder (ADHD) diagnosis. The statistical models were the same as for the main analysis of the primary outcome, with the addition of a fixed effect of the comorbidity (anxiety or ADHD) and an interaction between the comorbidity and study arm. A separate full economic evaluation will be conducted at the end of the 18-month follow-up (Phase 2) as the follow-up duration of 6-months is insufficient for calculating an incremental cost per quality-adjusted life year (QALY) gained. Here we explore the cost of delivering the ERP and psychoeducation interventions, examine relevant healthcare resource use, and

evaluate the suitability of the CHU9D for calculating QALYs in an 18-month analysis.

Further details on the method and findings can be found in the appendix (p7-23).

Role of the funding source

The study was publicly funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment (Ref: 16/17/02). The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

RESULTS

Participant enrolment began on 8th May 2018 and ended 30th September 2019. The last participant completed the 6-month follow-up on 30th April 2020; at this point Phase 1 of the ORBIT trial was completed. Of the 445 potential participants who registered their interest in the trial, 210 were excluded following an initial telephone screen and/or DAWBA results, thus 235/445 (52.8%) attended a baseline assessment and were consented into the trial. Eleven were found ineligible after the further screening measures; thus 224/445 (50.3%) potential participants were randomised, of whom 112/224 were assigned to the ERP intervention and 112/224 were assigned to the psychoeducation group. Figure 1 shows the flow of participants through the trial.

<<Insert Figure 1>>

Participants had a mean age of 12 years, were predominately male (79%) and defined their ethnicity as white (87%). Only 13% of participants were receiving medication for tics (Table

1). Baseline scores on the primary and secondary outcome measures were similar across the trial arms (Table 2).

<<Insert Table 1>>

<<Insert Table 2>>

Primary outcome data were collected from 99/112 (88.4%) in the intervention group and 105/112 (93.7%) in the psychoeducation group. The only predictor of missingness was site, which was included as a covariate in the statistical model.

Mean YGTSS-TTSS at 3 months in the ERP group was 23.9 (SD: 8.2) compared to 26.8 (SD: 7.3) in the psychoeducation group. The mean total decrease YGTSS-TTSS at 3-months was 4.5 (16%) for ERP vs 1.6 (6%) for psychoeducation, and at 6 months was 6.9 (24%) for ERP vs 3.4 (12%) for psychoeducation. The adjusted (for baseline and site) analysis of the primary outcome at 3 months revealed that the ERP intervention reduces YGTSS-TTSS by 2.29 points (95% CI: -3.86 to -0.71; $p=0.005$) in comparison to the psychoeducation with an effect size (ES) of -0.31 (95% CI -0.52 to -0.10) (Table 3; Figure 2).

<<Insert Table 3>>

<<Insert Figure 2>>

This adjusted effect on tics (YGTSS-TTSS) was slightly increased at 6 months (estimated difference: -2.64; 95% CI: -4.56 to -0.73) with an ES of -0.36 (95% CI -0.62 to -0.10). Figure 3 presents a forest plot of standardised effect sizes for primary and secondary outcomes.

The secondary outcome of parent reported tic (PTQ) symptoms supported the primary outcome finding at 3 months (-9.44; 95% CI: -15.37 to -3.51) and 6 months (-8.60; 95% CI: -14.43 to -2.77). There was no statistically significant difference in tic related impairment as measured by the YGTSS impairment scale at either time point (Table 3). Further, unplanned

analysis of the YGTSS-TTSS separately for motor and vocal tics replicated the pattern of the primary outcome showing greater improvement in the ERP group at 3 months (-1.28; 95% CI: -2.07 to -0.49) and 6 months (-1.19; 95% CI: -2.20 to 0.17) for motor tics. For vocal tics, this only reached statistical significance at 6 months (-1.56; 95% CI: -2.28 to -0.29).

Other secondary outcomes including parent-reported general emotional and behavioural functioning (SDQ), young person reported low mood (MFQ) and outcome assessor reported overall functioning (CGAS) were not significantly different between the two groups at 3 or 6 months. Although there was no difference in young person reported anxiety (SCAS) at 3 months, there was a difference in favour of the ERP group at 6 months (-5.10; 95% CI: -9.70 to -0.50). Conversely, the young person reported tic-specific quality of life (C&A-GTS-QOL) and the outcome-assessor completed perception of global improvement (CGI-I) showed superior results in the ERP group than psychoeducation at 3 months (CGI -0.41; 95% CI: -0.71 to -0.11. C&A GTS-QOL -4.81; 95% CI: -8.79 to -0.83) but no difference at 6 months.

<<Insert Figure 3>>

There was no difference in scores on the MFQ or PTQ at the mid-point of the intervention (see appendix p.24). A further unplanned analysis revealed no evidence to suggest that the ERP therapy had a different effect either in participants with or without a comorbid anxiety disorder or with or without comorbid ADHD (see appendix p24). An additional unplanned analysis (see Table 4) comparing positive treatment response as defined by a rating of 1 or 2 (very much/much improved) on the CGI-I, showed a significantly greater treatment response with ERP at 3 months (36% [95% CI 26-45], n=101) than for psychoeducation (20% [95% CI 12-28], n=100), OR 2.22 (95% CI: 1.17 to 4.20). This superior treatment response was sustained at 6 months for ERP (47% [95% CI 37- 57], n=93) compared to psychoeducation

(29% [95% CI 20-39], n=93), OR 2.20 (95% CI: 1.20 to 4.04). Table 4 shows there was a higher number of responders at both time points in the ERP group.

<<Insert Table 4>>

Two serious adverse events (SAE) were recorded during the trial, affecting two participants who were both in the psychoeducation group. Both SAEs were reviewed by the independent TSC and DMC and deemed unrelated to trial participation. There were slightly fewer AEs in the ERP group compared to psychoeducation (359 vs 433) and fewer participants in the ERP group experienced one or more adverse events (n=88/112; 79%) than in the psychoeducation group (n=94/112; 84%); see appendix p6 for further details.

Overall, engagement with the intervention was high in both groups, with minimum treatment completion (≥ 4 chapters) rates of 88% (99/112) in the ERP group and 94% (105/112) in the psychoeducation group. Similarly, number of log-ins were comparable across both groups, although Table 5 shows slightly higher number of log-ins for the participants in the ERP group. Perception of treatment suitability and credibility were also high across both groups (see Table 5). Approximately 15 minutes more therapist time was spent supporting the participants in the ERP group compared to the psychoeducation, however, therapist time required to effectively support the intervention was low at approximately 2.5 hours contact time per participant, approximately 15 minutes per week (combined child/young person and parent/carer contact time).

<<Insert Table 5>>

The fixed yearly cost of delivering the intervention was £103.64 per participant (calculated on £8494 yearly cost of the BIP platform and total cost of supervision and training at

£14719.78). As both interventions were delivered on the same platform there was no difference in fixed costs.

A variable cost was also calculated at £0.17 for each time a participant or one of their parents logged in to account for the SMS notification. Table 6 shows there was a small but significant difference between the two groups in the variable costs of the platform resulting from more platform logins and slightly more therapist contact time in the ERP intervention group (see appendix p 12-14 and table 6). There were no significant differences in wider health care costs (see appendix). Combining fixed and variable costs and including wider health care costs delivering the ERP intervention cost £159 (95% CI -£-£53 to £370), per participant compared to the psychoeducation group.

<<Insert Table 6>>

DISCUSSION

To our knowledge, ORBIT is the first adequately-powered, randomised, controlled trial of an online internet-delivered behavioural intervention for tics in children and adolescents, and the largest trial of any behavioural treatment for tics. The results support the clinical efficacy of online delivery of therapist-supported behavioural intervention for tics. The trial recruited ahead of time and target, reflecting a significant unmet treatment need in the population. Retention to the primary outcome at the primary endpoint (90%) and 6-month follow-up (>80%) were excellent. Acceptability and safety of the intervention was high. Analysis of our primary outcome (tic severity at 3 months post-randomisation) indicated a significant effect in favour of therapist-supported ERP compared to supported psychoeducation. Importantly, the therapeutic effect was durable and slightly increased at 6-months follow-up. Compared with the psychoeducation comparator, participants were twice as likely to show a positive

treatment response with the ERP intervention with just under half (47%) having responded positively by 6-month follow-up.

The participants in this trial had a moderate to severe level of baseline tic severity (mean YGTSS-TTSS 28.4 SD 7.7), which is approximately half a standard deviation higher than reported in previous face-to-face behavioural treatment trials.^{2,5} The trial design minimised the clinical comorbidity exclusions, resulting in a sample broadly representative of real-world clinical practice, and included participants with autism spectrum disorder (ASD), a group usually excluded in similar behavioural intervention trials. In the behavioural intervention group, just under one third had a co-existing anxiety disorder and just under one quarter had ADHD. The reduction in tics associated with the behavioural intervention was similar in those with and without co-existing anxiety and ADHD diagnoses. A relatively small proportion of participants (13%) were concurrently receiving tic medication. A further strength of the design was the inclusion of an active comparator arm controlling for non-specific effects of therapist contact, homework assignments, and online access. The uptake of both the ERP and psychoeducation was excellent.

In our previous systematic review,² we identified two superiority trials of face-to-face behavioural therapy (HRT/CBIT) for tics (N = 133) with evidence of a medium-sized effect in improving tics in favour of behavioural therapy (HRT/CBIT) when compared to waitlist/supportive psychotherapy (pooled effect size 0.64; 95% CI 0.29-0.99).^{2,4} The magnitude of effect of this online ERP is about half the size reported from previous superiority trials of face-to-face behaviour therapy for tics.² However, it is difficult to make direct comparisons of therapeutic efficacy with previous trials of face-to-face behavioural therapy given that this trial had a higher level of baseline tic severity, fewer co-morbidity exclusions, a lower proportion of participants receiving tic medication, longer follow-up and a potent active comparator. In practice, the direct comparison of efficacy may also be

misleading with respect to implementation because the purpose is not to replace face-to-face therapy, but to allow this scarce resource to be better targeted to those who need it most and to offer an effective online intervention to a much larger population of children/adolescents who are currently unable to access any behavioural treatment for tics.

A major difference between online delivery and face-to-face behavioural therapy for tics is the reduced amount of therapist time, required skill level of the therapist and cost. The total therapist contact time in the current trial was around 2.5 hours compared to 9-10 hours in comparable evidence-based face-to-face behavioural therapy for tics. Given the shortage of highly trained therapists with expertise in tic disorders and limited access to behavioural therapy, online delivery of behavioural therapy for tics has the potential to greatly expand the reach of effective behavioural interventions. From a public health perspective, with more efficient use of therapist time it should be possible to treat four people for every one person treated with face-to-face therapy. In addition, the requirement for less experienced therapists to support online behavioural therapy should expand the potential pool of therapists and thereby further extend the availability of online delivered behavioural therapy for tics. A further strength of the online delivery model is that fidelity of therapeutic content is built into the intervention, making transfer to real-world effectiveness much less susceptible than in traditional face-to-face therapy to therapeutic drift and the skill level of individual therapists.

Although a full economic evaluation of the intervention was conducted, the limited follow-up duration of 6-months meant that a meaningful incremental cost per QALY analysis in line with guidance could not be conducted as it would not capture the full benefits of the intervention. A further naturalistic follow-up of this trial to 18-months (Phase 2) is being conducted which will be used to calculate cost and QALYs over a longer time horizon.

Further implementation research will also be required to determine how best to integrate online behavioural therapy for tics within treatment pathways. For example, digital/online

delivery may work best as a first-line behavioural intervention with non- or poor responders being 'stepped-up' to more intensive face-to-face therapy. A further model to evaluate would be the 'blending' of online and face-to-face therapy for more complex cases, thereby reducing the overall number of face-to-face sessions required.

While an economic evaluation including QALYs is required to provide comparable evidence of cost-effectiveness, evidence from this trial suggests that implementation of online therapist-supported behavioural therapy has a high probability of cost-effectiveness for reduction in tic symptoms, with a non-significant increase in costs, and the potential to greatly increase the availability of effective behavioural treatment for children and adolescents with tic disorders.

RESEARCH IN CONTEXT PANEL

Evidence before this study:

In 2016 we conducted a systematic review of interventions for children and adolescents with tic disorders. 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. This search identified two randomised controlled trials (RCTs) of habit reversal training (HRT)/comprehensive behavioural intervention (CBIT) (SMD = 0.64;

95% CI 0.99-0.29; N = 133). In 2020, we updated this search and found no new trials of behavioural interventions for tics in children and adolescents. In 2017, we conducted a meta-review of scoping, narrative, systematic or meta-analytical reviews investigating the effectiveness of digital health interventions (DHIs) for mental health problems in children and adolescents. We also updated a systematic review of randomised controlled trials (RCTs) of DHIs for CYP published in the previous 3 years. The search was run on 11 online databases (Allied and Complementary Medicine, Ovid, MEDLINE, PsychINFO, PsychARTICLES, Embase, PubMed, ASSIA, Cochrane Library, CINAHL and Web of Science), and a limited keyword search was also performed on the JMIR Publications database. The search identified 30 unique RCTs of digital health interventions, with no digital intervention studies identified that focussed on treatment of tic disorders.

We have previously reported that only one in five children and adolescents in the UK have access to structured behavioural interventions for tics, and of these, less than half receive a minimum effective dose of therapy. Widely accessible and effective online behavioural interventions for tics are urgently needed.

Added value of this study:

This is the first RCT, to our knowledge, that reports the clinical efficacy, safety and costs of an adequately powered therapist and parent-supported online behavioural intervention for tics in children aged 9 to 17 years. We demonstrated that this 10-week online intervention was highly acceptable, well tolerated, and effective in reducing tics. The magnitude of the effect on tic reduction was durable with a slightly greater effect 3 months after treatment ended (6-month follow-up). Approximately a quarter of the therapist contact time is required compared to face-to-face behaviour therapy.

Implications of all the available evidence:

Data from this trial supports the implementation of online delivered behavioural therapy for tics as an efficient approach to increase the population reach of an effective treatment for children and adolescents with tic disorders. Further research is needed to determine the optimum care pathways with respect to sequencing and integration of digital and face-to-face behavioural therapy for tics in children and adolescents.

Contributors

CH was the chief investigator and conceived the study. The study design was conceived and written by CH, CLH, PA, TM, DM-C, EM, LM, IS, ES, RJ, RH, and CG. CLH wrote the trial protocol with input from all co-authors. CH, CLH, EM, SB, TM, CS, BJB were responsible for study implementation and general project management. BJB, CS, KK, CM were responsible for recruitment and follow-ups. TM and JK provided therapist supervision. LRC, EBD, AE, NK were the trial therapists. CLH oversaw trial management. LM and RJ designed and wrote the statistical analysis plan. RJ and LM conducted the analysis. RH designed the economic evaluation; RH and MLN wrote the health economic analysis plan. MLN and RH conducted the economic evaluation. CLH and CH drafted the original manuscript. All authors contributed to the interpretation of the data and re-drafts. All authors had full access to the study data and take responsibility for the integrity and accuracy of the data. CH is guarantor.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form. Aside from receiving funding from NIHR to support their salaries CLH, LM, EBD, RJ, KK, BJB, CS, CM, ES, PA, TM, IS, JK, RH, MLN, AE, LRC, NK, SB, CG, EM declare no conflict of interests. CH declares he was Principal Investigator on a grant from the National Institute of Health Research (NIHR) Health Technology Assessment programme to conduct an Evidence

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Data sharing agreement

Will individual participant data be available (including data dictionaries)?

Yes

What data in particular will be shared?

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices).

What other documents will be available?

Study protocol, statistical analysis plan, informed consent form, patient information sheets.

When will data be available (start and end dates)?

Beginning 3 months and ending 5 years following article publication.

By what mechanism will data be made available?

Proposals should be directed to primint@ucl.ac.uk to gain access, data requestors will need to sign a data access agreement.

With whom?

Researchers who provide a methodologically sound proposal

For what types of analyses?

To achieve aims in the approved proposal.

Preprint not peer reviewed

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Tables

Table 1. Baseline characteristics of participants

	Psychoeducation (control) (N = 112) N (%)	ERP (intervention) (N = 112) N (%)
Age at randomisation (years) – Mean (SD)	12.4 (2.1)	12.2 (2.0)
Gender		
Male	87 (78%)	90 (80%)
Female	25 (22%)	22 (20%)
Ethnicity		
White	99 (88%)	96 (86%)
Asian	3 (3%)	7 (6%)
Black	0 (0%)	1 (1%)
Mixed	7 (6%)	3 (3%)
Other	1 (1%)	0 (0%)
Not given	2 (2%)	5 (4%)
Main caregiver in trial		
Mother	101 (90%)	93 (83%)
Father	10 (9%)	16 (14%)
Grandmother	1 (1%)	1 (1%)
Other	0 (0%)	2 (2%)
Mother's highest educational level		
No qualifications	1 (1%)	3 (3%)
Mandatory secondary education (eg. GCSEs)	17 (15%)	16 (14%)
Further education (eg. A levels, BTEC, NVQ)	32 (29%)	33 (29%)
Higher education (eg. BA, BSc)	46 (41%)	46 (41%)
Post graduate education (eg. MA, MSc, PhD)	16 (14%)	14 (13%)
Father's highest educational level		
No qualifications	5 (4%)	2 (2%)
Mandatory secondary education (eg. GCSEs)	29 (26%)	29 (26%)
Further education (eg. A levels, BTEC, NVQ)	33 (29%)	35 (31%)
Higher education (eg. BA, BSc)	34 (30%)	32 (29%)
Post graduate education (eg. MA, MSc, PhD)	11 (9%)	14 (13%)

	Psychoeducation (control) (N = 112) N (%)	ERP (intervention) (N = 112) N (%)
Mother's occupational status		
Not in work / unemployed	22 (20%)	19 (20%)
Lower occupational status [§]	26 (23%)	24 (21%)
Higher occupational status ^{§§}	57 (51%)	65 (58%)
Other	7 (6%)	4 (4%)
Father's occupational status		
Not in work / unemployed	4 (4%)	2 (2%)
Lower occupational status	30 (27%)	33 (29%)
Higher occupational status	67 (60%)	65 (58%)
Other	10 (9%)	12 (11%)
Tic typology		
Both motor and vocal tics	106 (95%)	103 (92%)
Motor tics only	6 (5%)	9 (8%)
Vocal tics only	0 (0%)	0 (0%)
Comorbidities		
Anxiety disorder	27 (24%)	34 (30%)
Attention deficit hyperactivity disorder (ADHD)	25 (22%)	26 (23%)
Oppositional defiant disorder (ODD)	23 (21%)	26 (24%)
Autism spectrum disorders	4 (4%)	9 (8%)
Obsessive compulsive disorder (OCD)	3 (3%)	8 (7%)
Major depression	6 (5%)	2 (2%)
Conduct disorder	2 (2%)	3 (3%)
Bipolar disorder
Taking any tic medication*	16 (13%)	14 (13%)
Centre		
Nottingham	57 (51%)	57 (51%)
London	55 (49%)	55 (49%)

Notes: Statistics are n (%) unless otherwise specified. SD = standard deviation. Percentages are given to the nearest whole number. Comorbidities are based on $\geq 50\%$ probability of having a DSM-IV / DSM 5 diagnosis as assessed by the Development and Wellbeing Assessment (DAWBA). Anxiety disorders include separation anxiety, specific phobias, social phobia, panic disorder, agoraphobia and post traumatic stress disorder (PTSD). Diagnoses are not mutually exclusive and so percentages are not expected to total 100%. Denominators for percentages for comorbidities are not always the full sample, because insufficient information was supplied for some participants to make either a positive or negative diagnosis. Insufficient information was supplied to assess bipolar disorder for all participants. *Any tic medication included: Clonidine, Risperidone, Aripiprazole, Haloperidol, Guanfacine, Topiramate. [§]Lower occupational statuses are defined as manual or semi-manual occupations. ^{§§}Higher occupational statuses are defined as professional occupations. ERP = exposure and response prevention.

Table 2. Primary and secondary outcomes at baseline

	Psychoeducation (control) (N = 112) Mean (SD)	ERP (intervention) (N = 112) Mean (SD)
Primary outcome		
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	28.4 (7.1)	28.4 (7.7)
Secondary outcomes		
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	22.9 (9.9)	23.8 (10.3)
Parent Tic Questionnaire (PTQ)	53.1 (26.1)	54.7 (29.9)
Children's Global Assessment Scale (CGAS)	72.1 (11.8)	70.7 (13.7)
Strengths and Difficulties Questionnaire (SDQ)	16.3 (6.2)	18.0 (6.5)
Mood and Feelings Questionnaire (MFQ)	15.9 (11.5)	16.3 (11.3)
Spence Child Anxiety Scale (SCAS)	30.5 (17.9)	32.9 (20.2)
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	35.0 (17.2)	36.6 (16.4)

*Notes: Statistics are mean (SD) unless otherwise specified and are calculated for all available data. SD = standard deviation. Higher scores on the C&A-GTS-QOL indicate **worse** quality of life. There was 1 missing value for the SCAS scale. All other measures were complete. ERP = exposure and response prevention.*

Table 3. Effect of the behavioural therapy intervention on primary and secondary outcomes at 3 and 6 months follow up

	3 months follow up (primary endpoint)			6 months follow up		
	Psychoeducation (control) (N = 112) Mean (SD)	ERP (intervention) (N = 112) Mean (SD)	Estimated difference (95% CI)	Psychoeducation (control) (N = 112) Mean (SD)	ERP (intervention) (N = 112) Mean (SD)	Estimated difference (95% CI)
Primary outcome						
Total Tic Severity Score (TTSS) on the Yale Global Tic Severity Scale (YGTSS)	26.8 (7.3)	23.9 (8.2)	-2.29* (-3.86 to -0.71)	25.0 (7.6)	21.5 (8.8)	-2.64* (-4.56 to -0.73)
Standardised effect size	-0.31* (-0.52 to -0.10)	-0.36* (-0.62 to -0.10)
Secondary outcomes						
Total Motor Tic Score on the Yale Global Tic Severity Scale (YGTSS)	15.1 (3.3)	13.6 (4.0)	-1.28* (-2.07 to -0.49)	14.1 (3.7)	12.7 (4.3)	-1.19* (-2.20 to -0.17)
Total Phonic Tic Score on the Yale Global Tic Severity Scale (YGTSS)	11.7 (5.0)	10.2 (5.3)	-1.05 (-2.13 to 0.02)	10.9 (5.3)	8.8 (5.7)	-1.56* (-2.8 to -0.29)
Impairment score on the Yale Global Tic Severity Scale (YGTSS)	19.1 (10.9)	16.7 (10.4)	-2.24 (-4.82 to 0.33)	17.0 (10.5)	14.7 (10.7)	-1.95 (-4.68 to 0.78)
Parent Tic Questionnaire (PTQ)	45.7 (25.5)	34.7 (26.4)	-9.44* (-15.37 to -3.51)	40.6 (24.3)	31.1 (21.6)	-8.60* (-14.43 to -2.77)
Clinical Global Impression Scale – Improvement (CGI-I)	3.37 (1.11)	2.96 (1.1)	-0.41* (-0.71 to -0.11)	3.1 (1.1)	2.8 (1.3)	-0.31 (-0.66 to 0.03)

	3 months follow up (primary endpoint)			6 months follow up		
	Psychoeducation (control) (N = 112) Mean (SD)	ERP (intervention) (N = 112) Mean (SD)	Estimated difference (95% CI)	Psychoeducation (control) (N = 112) Mean (SD)	ERP (intervention) (N = 112) Mean (SD)	Estimated difference (95% CI)
Children's Global Assessment Scale (CGAS)	75.2 (12.6)	75.9 (12.6)	0.96 (-1.48 to 3.41)	76.8 (12.3)	77.5 (14.7)	0.60 (-2.24 to 3.44)
Strengths and Difficulties Questionnaire (SDQ)	14.2 (6.3)	14.7 (6.1)	-0.38 (-1.62 to 0.85)	13.3 (6.1)	15.3 (6.2)	0.57 (-0.93 to 2.07)
Mood and Feelings Questionnaire (MFQ)	12.6 (11.1)	10.7 (11.1)	-1.36 (-3.75 to 1.02)	11.4 (11.2)	11.4 (12.1)	-0.61 (-3.85 to 2.64)
Spence Child Anxiety Scale (SCAS)	28.2 (18.3)	27.2 (19.0)	-2.80 (-6.52 to 0.93)	25.9 (18.7)	25.7 (19.6)	-5.10* (-9.70 to -0.50)
Child and Adolescent Gilles de la Tourette Syndrome–Quality of Life Scale (C&A-GTS-QOL)	31.8 (17.7)	25.7 (18.0)	-4.81 (-8.79 to -0.83)	28.9 (18.3)	27.4 (16.5)	-2.91 (-7.60 to 1.78)

Notes: Statistics are mean (SD) unless otherwise specified. SD = standard deviation. CI = confidence interval. *Indicates statistically significant result. Statistical models adjusted for the baseline measure of the outcome in question (with the exception of the CGI-I) and site. For the standardised effect size, YGTSS-TTSS was standardised by the pooled mean and SD at baseline. Higher scores on the C&A-GTS-QOL indicate **worse** quality of life. At 3 months follow up, there were 12 missing observations (11%) for the primary outcome in the ERP arm compared to 11 (10%) in the psychoeducation arm. The quantity of missing data for secondary outcomes was similar in both trial arms. ERP = exposure and response prevention.

Table 4. Response to treatment at 3 and 6 months follow-up

	3 months follow up			6 months follow up		
	Psychoeducation (control) (N = 100) N (%)	ERP (intervention) (N = 101) N (%)	Odds ratio (95% CI)	Psychoeducation (control) (N = 93) N (%)	ERP (intervention) (N = 93) N (%)	Odds ratio (95% CI)
CGI-I scored indicating 'much' or 'very much' improved (responded to treatment)	20 (20%)	36 (36%)	2.22* (1.17 to 4.20)	27 (29%)	44 (47%)	2.20* (1.20 to 4.04)
Change in response between 3 and 6 months						
No response to treatment at either time	56 / 93 (60%)	37 / 90 (41%)	..
Response at both time	9 / 93 (10%)	23 / 90 (26%)	..
New responder at 6 months	18 / 93 (19%)	20 / 90 (22%)	..
Relapsed responder at 6 months	10 / 93 (11%)	10 / 90 (11%)	..

*Notes: Statistics are frequency (N) and percentage (%) unless otherwise specified. *Indicates statistically significant. CGI-I = Clinical Global Impressions – Improvement. CI = confidence interval. Statistical models adjusted for site. ERP = exposure and response prevention.*

Table 5. Engagement with the intervention and perception of treatment suitability and credibility

	Psychoeducation (control) (N = 112)	ERP (intervention) (N = 112)
Young person met therapist – N (%)	86 (77%)	80 (71%)
Treatment suitability and expectation of improvement (credibility) – Median (IQR)		
Young person	6 (5 to 7)	7 (6 to 8)
Supporting parent/caregiver	5 (4 to 6)	6 (5 to 7)
Completion of first four chapters of intervention (adherence) – N (%)		
Young person	105 (94%)	99 (88%)
Supporting parent/caregiver	103 (92%)	95 (85%)
Number of chapters of intervention completed (dose) – Median (IQR)		
Young person	9 (7 to 10)	8 (6 to 10)
Supporting parent/caregiver	10 (8 to 10)	9 (5 to 10)
Number of logins – Median (IQR)		
Young person	13 (10 to 18)	19 (10 to 28)
Parent/ carer	17 (12 to 24)	18 (12 to 27)
Therapist time on platform in minutes		
Young person	55.6 (27.1)	59.2 (29.2)
Parent/carer 1	74.2 (34.4)	83.9 (42.8)
Parent/ carer 2	0.4 (2.1)	1.0 (7.2)
Therapist time on phone in minutes		
Young person	0.1 (0.3)	0.2 (1.8)
Parent/ carer 1	3.5 (7.5)	3.7 (6.4)
Parent/ carer 2	0.3 (2.0)	0.2 (1.9)
Total therapist time in minutes	133.9 (55.1)	148.2 (64.9)
Platform logins		
Young person	14.6 (8.6)	19.8 (10.9)
Parent/ carer 1	18.1 (9.0)	20.4 (11.5)
Parent/ carer 2	1.6 (2.6)	6.8 (8.7)

Notes: Statistics are as specified. IQR = interquartile range. Treatment completers defined as young person completion of first four chapters. ERP = exposure and response prevention.

Table 6. Comparison of variable costs between the psychoeducation (control) and ERP (intervention) group across the 6 months

	Psychoeducation (control) (N = 111)	ERP (Intervention) (N = 111)	Difference at 6 months £ (95% CI)
	Mean (SD) £	Mean (SD) £	
Cost of therapist contact time			
Young person	16 (9)	18 (9)	
Parent/ carer 1	22 (10)	25 (13)	
Parent/ carer 2	0.09 (0.56)	0.20 (2)	
Total	38 (17)	43 (20)	4.99* (0.01 to 9.96)
Login costs			
Young person	3 (1)	3 (2)	
Parent/ carer 1	3 (2)	3 (2)	
Parent/ carer 2	0.01 (0.10)	0.04 (0.33)	
Total	6 (3)	7 (4)	1.25* (0.46 to 2.04)
Total variable costs	44 (18)	50 (22)	6.27 (0.88 to 11.67)

*Note: *Indicates statistically significant. CI = confidence interval. ERP = exposure and response prevention.*

Figure 1. Trial recruitment and retention

Note.
 BT=behavioural therapy. CAIDS-Q = Child and Adolescent Intellectual Disability Screening Questionnaire. DAWBA = development and well-being assessment. DSH = deliberate self-harm. ERP = exposure and response prevention. PIC = participant identification centre. YGTSS = Yale Global Tic Severity Scale. Follow-up rate given as number (%) completing primary outcome measure.
 * completed ≥ 4 chapters





