

Great Ormond Street Hospital for Children



NHS Foundation Trust

Treatment and Management - pharmacological

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Pharmacological considerations – talk outline

Medication is part
of holistic
intervention
package

Medication for tics

Medication for co-
morbidities

Clinical
considerations

Formulation
Considerations

Future options

Information for young people and families

Information for young people and families



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Information for young people and families



Information for young people and families



Information for young people and families



Factors to consider when thinking about medication

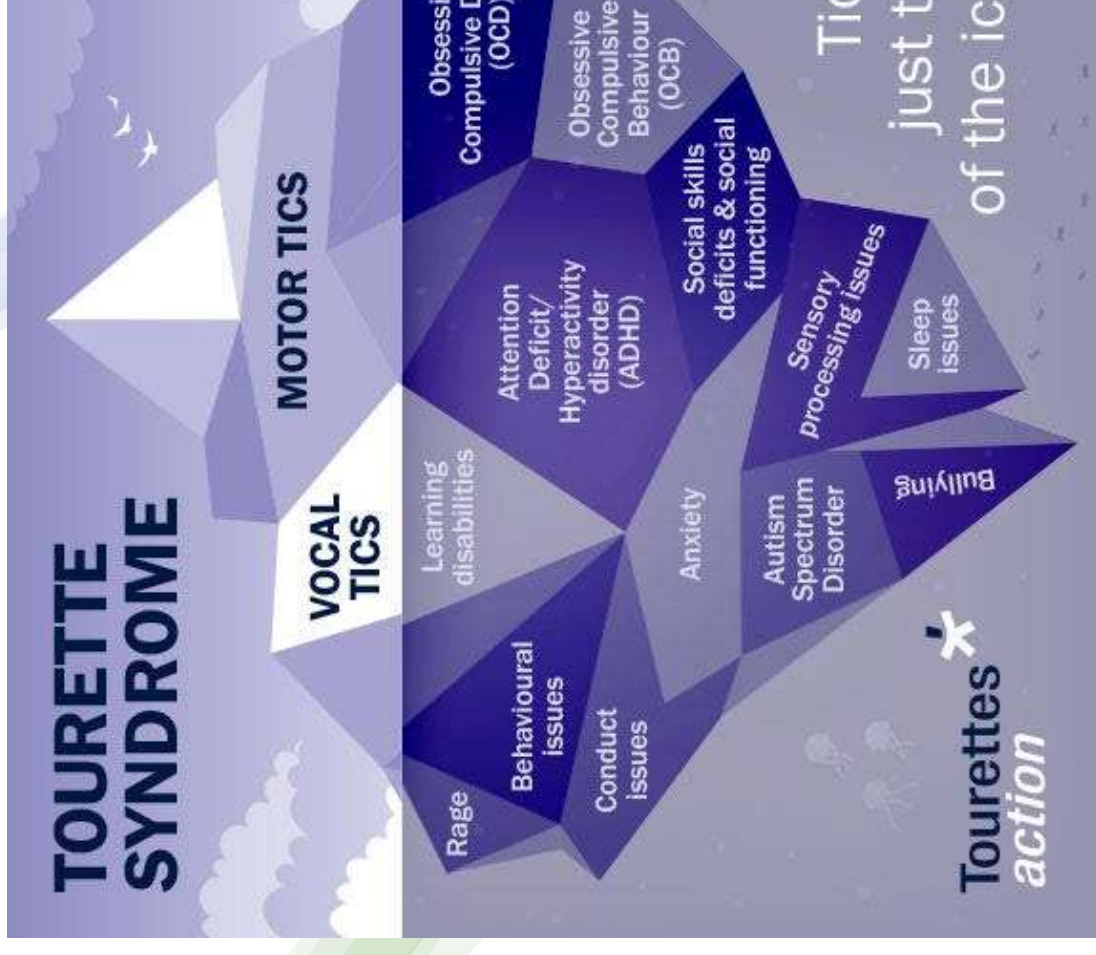
- Symptom severity and impact – the majority of children will not require medication for tics. Possible indications include interference with daily functioning, pain, social problems, bullying, impact on learning.
- Who wants medication?
- Target tics or co-morbidity?
- Cost-benefit of medication
- Expectation management
- Formulation accuracy?
- Prescribing plan and therapeutic trials – remember that tics wax and wane, therefore need long observation periods, response depends on natural phase.
- Reviewing, monitoring and discontinuation

A word on Therapeutic assessment

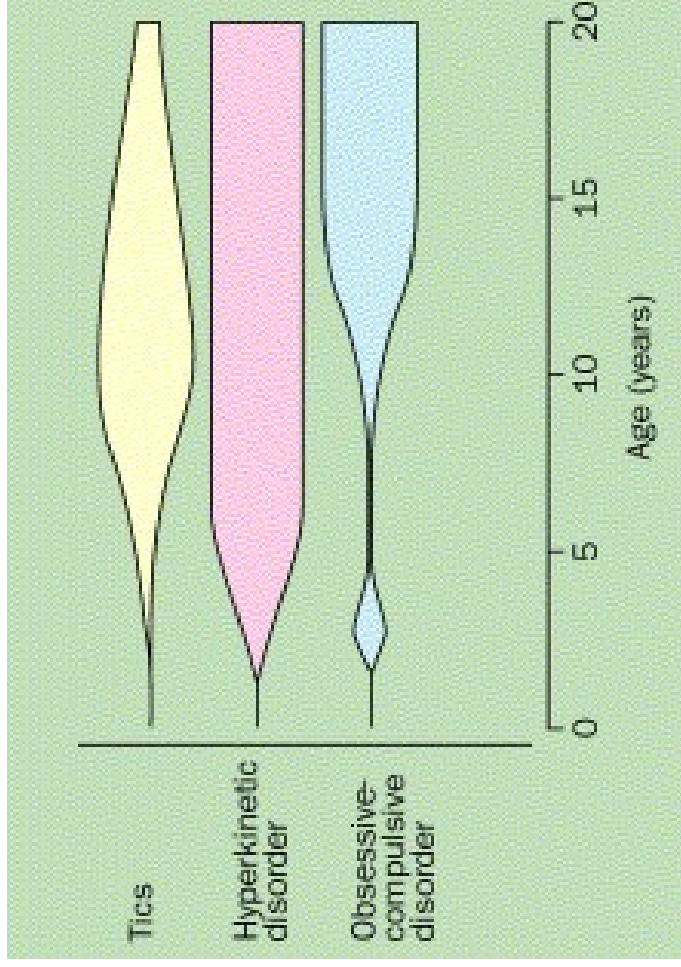
- Establish symptom severity and impact
- Establish who wants treatment – give children a voice
- Establish if main problems pertain to tics or co-morbidities – if possible allow families to come to this conclusion themselves
- Differentiate functional tics

Target Tics or Co-morbidity?

- Phenotypic data from genetic studies of people with TS > 6 years
- 1300 participants with TS
- 86% met criteria for one or more comorbid disorder
- 58% met criteria for two or more



Co-occurring conditions



- OCD - 50% - more common in females
- ADHD – 50-70% - more common in males
- Triad of TS/ ADHD and OCD seen in 30%
- Also: mood disorders, other anxiety disorders, ASD
- Children more likely to have ADHD
- Adolescents/ adults- more likely to have OCD
- anxiety disorders - ?undiagnosed ADHD



Understanding disability in Tourette Syndrome

PRINGSHEIM et al 2008
Dev Med Child Neurol

- 71 children age 7-17 with TS
- Parents completed CHQ
- For children with TS only, psychosocial health = normal controls in most domains
- TS + ADHD, TS + OCD and TS + ADHD + OCD significantly impaired in all domains
- Variable which most strongly predicted impairment was ADHD severity

Medical Management of Tourettes syndrome - Available Guidance

- No NICE guidance
- 2011 - ESSTS – European Guidelines
- 2012 Canadian guidelines – Pringsheim et al
- 2016 – Health Technology Assessment (HTA) systematic review
- 2019 American Academy of Neurology guidelines
- 2021- European Clinical Guidelines – version 2.0 published in part



AAN Practice Guidelines 2019

- Psychoeducation child & family
- Psychoeducation teacher & classroom
- Assessment & Treatment of ADHD
- Assessment & Treatment of OCD & other Co-morbidities
- Assessment of tic severity & expectation management
- Behavioural Treatment
- Pharmacological Options
- Interventions for adults



Medication Options

Alpha agonists – clonidine, guanfacine

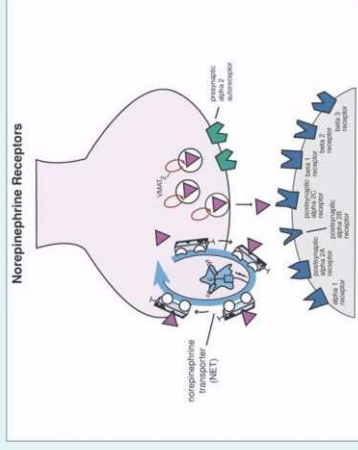
Antipsychotics - risperidone, aripiprazole, haloperidol

Anticonvulsants - topiramate

Dopamine depletors - tetrabenazine

Others- benzodiazepines (rarely)

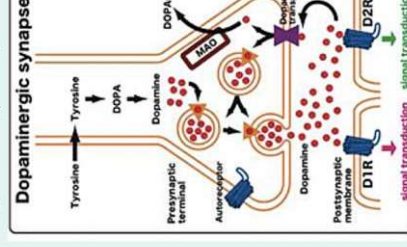
Noradrenaline



- No definite evidence for NA abnormality in TS
- α_2 noradrenergic agonist clonidine acts on somatodendritic autoreceptors
- Clonidine reduces tics by 0-50% in trials
- Guanfacine may be more selective for prefrontal cortex α_2 receptors (longer acting)

Dopamine

- No definite evidence for DA abnormality in TS
- Dopamine antagonists most effective anti-tic medication
- Efficacy correlates with potency of postsynaptic D2 receptor blockade
- Reasonable trial evidence for
 - Haloperidol
 - Pimozide
 - Sulpiride
 - Risperidone
 - Ziprasidone



Drug Actions

Summary: Systematic Review

National Collaborating Centre For Mental Health

- Noradrenergic agents (clonidine) and antipsychotics have similar efficacy – medium effect size
- Adverse effect profile favours noradrenergic agents over antipsychotics
- Atomoxetine – small statistical effect but unlikely to be clinically meaningful
- Stimulants – no evidence of tic worsening
- Habit reversal training (HRT) – clinically meaningful improvement – medium effect size. Moderating effects of medication unknown.
- No evidence of benefit for fish oils, acupuncture, TMS, DBS

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

Craig Whittington,¹ Mary Pennant,² Tim Kendall,² Cristine Glaser,³ Madeleine Groom,³ Tammy Hedderly,⁵ Isobel Heyman,⁶ Stephen Jackson,⁷ Tara Murphy,⁶ Hugh Rickards,⁸ Mary Robertson,⁹ and Chris Hollis³

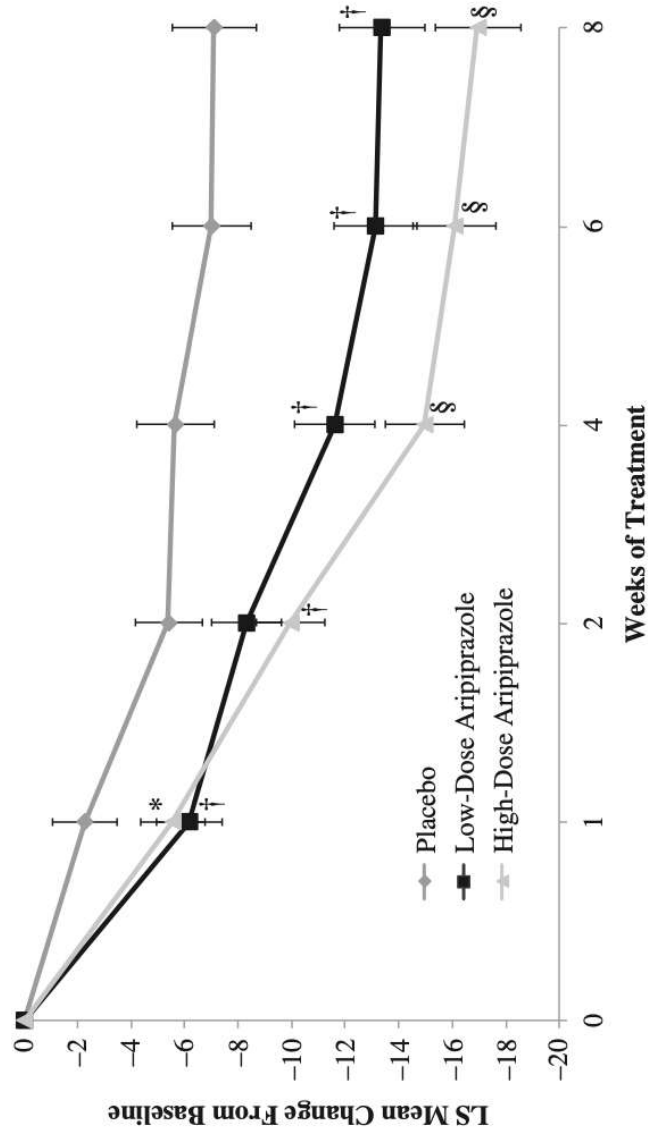
¹National Collaborating Centre for Mental Health, University College London, London; ²Centre for Mental Health, Royal College of Psychiatrists, London; ³Division of Psychological Science, University of Nottingham, Nottingham; ⁴School of Psychiatry, University of Manchester, Manchester; ⁵Paediatric Neurosciences, Evelina London Children's Hospital, London; ⁶Department of Child and Adolescent Mental Health, Great Ormond Street Hospital, London; ⁷Department of Child and Adolescent Mental Health, Great Ormond Street Hospital, London; ⁸School of Psychology, University of Nottingham, Nottingham; ⁹National Centre for Mental Health, University of Birmingham, Birmingham; ¹⁰Department of Neurology, St Georges Hospital, London

Background: Tourette syndrome (TS) and chronic tic disorder (CTD) affect 1–2% of children and young people. The most effective treatment is unclear. To establish the current evidence base, we conducted a systematic review of the literature. **Methods:** Databases were searched from 1966 to 2015 for placebo-controlled trials of pharmacological, behavioural, physical or alternative interventions for children and young people with TS or CTD. Certainty in the evidence was assessed with the GRADE tool. **Results:** 11 trials were included [pharmacological (32), behavioural (5), physical (2), dietary (1)]. For pharmacological trials, evidence favouring the intervention from four trials of α_2 -adrenergic receptor agonists (standardised mean difference (SMD) = -0.71 ; 95% CI -1.03 , -0.40 ; $N = 164$) and two trials

DBRCT

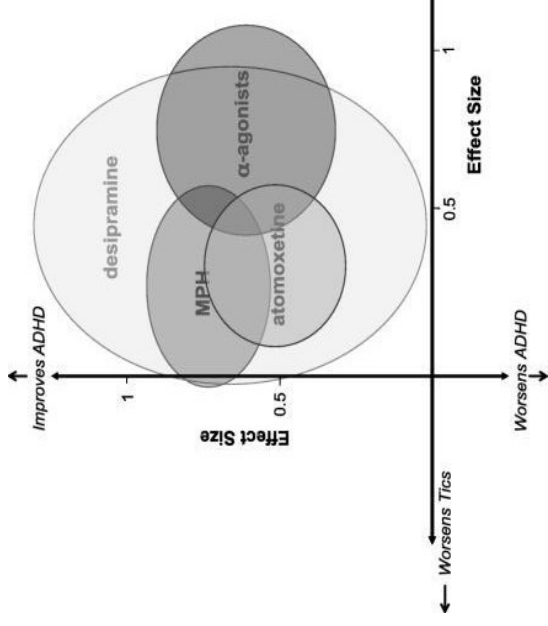
- Overall, a 45.9% and 54.2% decrease from baseline in total tic score (Sallee et al 2017)
- Low 5mg <50kg, 10mg >50kg; High 10mg <50kg, 20mg >50kg.

ORAL ARIPIPAZOLE FOR TOURETTE'S DISORDER



Treating ADHD in Tourette's

- ADHD may be most impairing symptoms
- Do stimulants exacerbate tics?
- Methylphenidate appears safe and effective in short term trials in children with tics (The TS Study Group, Neurology 2002, Gadow et al, 2007)
- The SATURN Trial: open label trial of Guanfacine vs Methylphenidate (Hollis et al)



Meta-Analysis: Treatment of Attention-Deficit/Hyperactivity Disorder in Children With Comorbid Tic Disorders

Bloch et al; JAACAP 2009

Medication choice should have symptom focus

- Best for ADHD: stimulants, try atomoxetine if stimulants not effective
- Some effect for ADHD and tics: guanfacine, clonidine
- Moderate effect on tics: guanfacine, clonidine, risperidone, aripiprazole
- Challenging behaviour in the context of LD or ASD: risperidone, aripiprazole
- Sleep: guanfacine, melatonin
- Functional tics, anxiety, OCD, depression: SSRI

Naloxone + other
opioids

Anti-androgen

Nifedipine

Nicotine,
mecamylamine

Benzodiazepines,
baclofen

Tetrabenazine

N-acetylcysteine
augmentation

Topiramate, Sodium
valproate,
Levetiracetam

Cannabinoids

Botulinum toxin

Immunomodulation,
penicillin
prophylaxis

Transcranial
magnetic
stimulation

Neurosurgery; deep
brain stimulation

Future Options

Cannabis based medications for tics

- Many TS patients use cannabis as self-medication for tics
- Current RCTs limited to THC in adults
- No RCT data for other cannabinoids
- Medical cannabinoids not yet proven treatment for TS
- Cannabis based medications not recommended for C/YP due to potentially harmful cognitive and affective outcomes/ risk of psychosis
- Clinician should be aware of safeguarding issues

Botulinum toxin

Used in older adolescents/ adults only

For localized and impairing simple motor tics especially 'whiplash tics'

Into laryngeal muscles for disabling and aggressive phonic tics- e.g. loud shouting / barking tic

Risks: weakness, hypophonia

Effects last a few months

Reduces urge to tic



Prognosis for Tourette's

Retrospective data:

- Peak tic severity age 10
- In general repertoire of tics decreases during adulthood
- Small minority have severe, persistent tics – most have a few, non-impairing tics

PANDAS/ PANS

Diagnostic criteria for PANDAS and PANS (Swedo et al 1998; Swedo et al 2012)

Guidelines for diagnosing PANDAS include:

1. Presence of OCD and/or tics, particularly multiple, complex or unusual tics
2. Age Requirement (Symptoms of the disorder first become evident between 3 years puberty)
3. Acute onset and episodic (relapsing-remitting) course
4. Association with Group A Streptococcal (GAS) infection
5. Association with Neurological Abnormalities (motor hyperactivity/adventitious movements including chorea)

Guidelines for diagnosing PANS; patients must have the following:

1. An abrupt, acute, dramatic onset of obsessive-compulsive disorder or severely restricted intake
2. Concurrent presence of additional neuropsychiatric symptoms with similarly severe onset from at least 2 of the following categories:
 - Anxiety
 - Emotional Lability and/or Depression
 - Irritability, Aggression, and/or Severe Oppositional Behaviors
 - Behavioral (Developmental) Regression
 - Sudden Deterioration in School Performance
 - Motor or Sensory Abnormalities
 - Somatic Signs and Symptoms, including Sleep Disturbances, Enuresis, or Urinary F
3. Symptoms are not better explained by a known neurologic or medical disorder
4. Age requirement – None

Evidence base for treatment of PANS/PANDAS- BPNA review

- OCD symptoms in PANDAS patients respond to CBT at a similar rate to response seen in t paediatric OCD
- No studies of SSRIs in PANS patients with OCD
- Tics- behavioural treatment effective, ant medications no studies
- Systematic review examined range of treatments in PANDAS patients
- Studies small, high risk of bias, very few RCTs
- No evidence for antibiotics or IVIG

EMTICS study- methods

- Prospective cohort study of 715 children with TS/CTD
- Average age 10.6 years, 77% male
- Bimonthly assessment of tics, OCD symptoms and ADHD symptoms
- Parents completed weekly structure diaries
- GAS exposure- throat swabs, serology ASOT, anti-DNAse antibody titres
- Tic exacerbations defined as 6 point on YGTSS – TTS score-tic exacerbation in addition to above

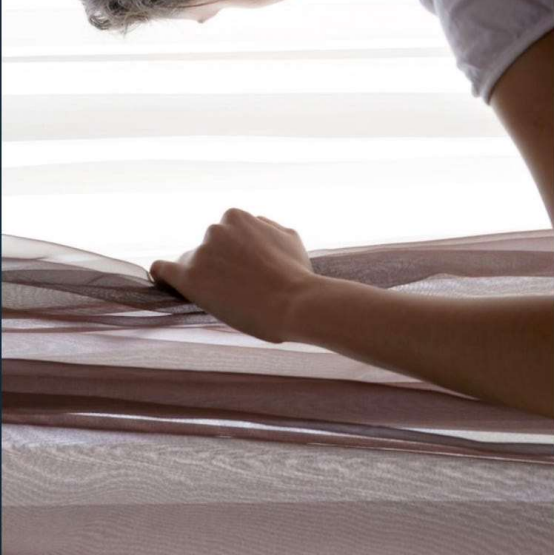
EMTICS study- results

- 405 exacerbations in 308 participants
- No significant association found for ongoing GAS exposure and tic exacerbations
- No association between GAS exposure and OC symptom severity
- Positive effect between GAS exposure and change in severity if hyperactivity/impulsivity symptoms ? Link between and behavioural patterns of motor hyperactivity as for rheumatic chorea
- Concluded that specific work up/management of GAS infection is unlikely to help modify the course of chronic tic disorder and is not recommended.

BPNA consensus statement-April 2021

- Recommends further work on validity of PANS/PANDAS as diagnostic entities
- Clinical overlap with paediatric OCD and tic disorders
- 2/3 show response to conventional MH interventions
- Recommends
 - MDT working across specialties recommended
 - Neurologists' role- assessment of neurological conditions that can be associated with acute neuropsychiatric presentations
 - Neurology support to discussion around treatments
 - CAMHS clinicians to assess mental health domains affected/ functional impairment
 - Treatment with antibiotics/immunomodulatory treatments not recommended as no evidence effective and can cause immunocompromise
 - Risk of diverting focus away from effective symptom directed treatments.

See all Life



‘We’ve seen so many girls suffering troubling rise of tics among teenagers

Parents and clinicians are reporting an increase in disorders and Tourette’s syndrome in teenagers

By Lauren Libbert

9 March 2021 • 11:24am



It was in July last year when Rachel’s* daughter light tingling sensation in her spine before beginning to shake her shoulders repetitively. What ensued over the course of several months was an acceleration of distressing vocal and motor tics that left her shaking herself in the face, kick out her legs, shake her head and even

THE SUNDAY TIMES

PRIVATE SCHOOL PAYLIST

BRITAIN'S BEST PAID TEACHERS

THE FASHION ISSUE

YOUR 100-PAGE NEW-LOOK STYLE MAGAZINE

Queen ‘won’t watch the Harry and Meghan circus’

- Angry courtiers threaten reprisals over TV interview
- Royals plan PR blitz to counteract couple's claims

Royal Household and The Dismissal
The Queen will not watch the Harry and Meghan interview, according to a source close to the royal household. The source said that the Queen is "not interested in the 'circus' that is being created around the couple's claims." The source also said that the Queen is "not interested in the 'circus' that is being created around the couple's claims."

NEWMAN'S VIEW



Teenage girls suffer 'explosion of tics' in lockdown

Home to Childhood Journal
The explosion of tics in teenage girls during lockdown is a phenomenon that has been widely reported. The phenomenon is thought to be linked to the stress and anxiety of lockdown. The phenomenon is thought to be linked to the stress and anxiety of lockdown.



The Queen at St George's Hall, Windsor Castle, with flags to mark Commonwealth Day. She will pay tribute to 'the family of nations' today
The Queen will pay tribute to 'the family of nations' today. The Queen will pay tribute to 'the family of nations' today. The Queen will pay tribute to 'the family of nations' today.

EXCLUSIVE

INSIDE THE PM'S ESN WARROOM

PM'S ESN WARROOM

Heyman, Liang, Hedderly Archives of Diseases in Childhood 2021

Tic attack vs Classic Tics (Demartini 2015, Ganos 2016)

FUNCTIONAL TICS	CLASSIC TICS
A sudden and later onset	Onset usually gradual, occurring at a young age and decreasing towards adulthood
Often don't respond to common drugs prescribed for classic tics	Tic severity often responds to medication / behavioural therapy
Often remit suddenly	Rarely remit suddenly
Associated with increased stress/recent events	Wax and waning pattern
Often runs in families	Often runs in families

Functional Tics

<https://adc.bmj.com/content/archdischild/early/2021/03/06/archdischild-2021-321748.full.pdf>

- Predominantly teenage girls (F:M >9:1)
- Average age 13.7yr
- Rapid onset of exaggerated tics – YGTSS average range)
- High incidence of coprolalia (54%) and specific large amplitude arm movements (85%)
- Rapid progression from simple to complex (92%) presentation
- Higher prevalence of 'belle indifference'
- High incidence of exposure to tics, TikTok (77%)
- High suggestibility and distractibility
- 91% comorbid mental health problems
- Prior history of mild tics in 44%
- History of anxiety 68%, prior possible functional
- History of symptoms of neurodevelopmental disorder (suspected 57% ASD, subsample at GOSH 50% diagnosed ASD)
- Family history of anxiety, neurodevelopmental disorder
- Few have history of Covid symptoms

Possible Aetiology

- Neurodevelopmental predisposition
- Known increase in anxiety during pandemic
- Those with undiagnosed neurodevelopmental difficulties are at increased risk of anxiety
- Those with neurodevelopmental difficulties are more at increased risk for functional symptoms
- Heightened anxiety in families during pandemic
- Contagion effects, secondary gain
- Implications for long Covid



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GOSH Tic Disorders Service

- Paediatrician or CAMHS referral
- Differentiation tics/ functional tics and co-morbidities
- Consultation & recommendations
- Group Psychoeducation
- Group ERP
- Limited neurodevelopmental assessment

Thank You & Questions

