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
Intervention Package

Before thinking about medication, the following should be put in place or considered:

- Psychoeducation – books, groups, individual psychoeducation
- School liaison – ensuring supportive school environment
- Assessment of co-morbidities, cognitive assessment
- Non-pharmacological interventions – HRT, ERT, CBIT, ORBIT
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

"Original Investigation
Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome"

Matthew E. Hirschtritt, MD, MPH; Paul C. Lee, MD, MPH; David L. Pauls, PhD; Yves Dior, MD; Marco A. Grados, MD; Cornelia Illingworth, PhD; Robert A. King, MD; Paul Sandor, MD; William M. McMahon, MD; Gillian J. Lyons, MD, PhD; Danielle C. Catt, MD, PhD; Roger Korlan, MD; Mary M. Robertson, MBChB, MD, DS(Med); FRCP; FRCPD; FRCChyr; Lisa DiGiacco, BA; Jeremiah M. Scharf, MD, PhD; Carol A. Mathews, MD, for the Tourette Syndrome Association International Consortium for Genetics"
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, disruptive behaviour 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
<table>
<thead>
<tr>
<th>Medication Options</th>
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<tr>
<td>Alpha agonists – clonidine, guanfacine</td>
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<td>Antipsychotics - risperidone, aripiprazole, haloperidol</td>
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<td>Anticonvulsants - topiramate</td>
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<td>Dopamine depletors - tetrabenazine</td>
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<td>Others - benzodiazepines (rarely)</td>
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Drug Actions

**Noradrenaline**
- No definite evidence for NA abnormality in TS
- $\alpha_2$ noradrenergic agonist clonidine acts on somatodendritic autoreceptors
- Clonidine reduces tics by 0-50% in trials
- Guanfacine may be more selective for prefrontal cortex $\alpha_2$ 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
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
- No evidence of benefit for fish oils, acupuncture, TMS, DBS

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

Craig Whittington, Mary Pennant, Tim Kendall, Cristine Gla Trayner, Madeleine Groom, Tammy Hedderly, Isobel Heyman, Stephen Jackson, Tara Murphy, Hugh Rickards, Mary Robertson and Chris Hollis

1National Collaborating Centre for Mental Health, University College London, London; Centre For Mental Health, Royal College of Psychiatrists, London; 2Division of Psychiatry School of Medicine, University of Nottingham, Nottingham; 3School of Psychological Sciences, University of Manchester, Manchester; 4Pediatric Neuroimaging, Evelina London Children’s Hospital, London; 5Department of Child and Adolescent Mental Health, Great Ormond Street Hospital, London; 6School of Psychology, University of Nottingham, Nottingham; 7National Centre for Neurodevelopmental Disorders, University of Birmingham, Birmingham; 8Department of Neurology, St George's Hospital, London.

Background: Tourette syndrome (TS) and chronic tic disorder (CTD) affect 1–2% of children, and 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 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 approach, and where possible, data were extracted from individual trials and combined with meta-analysis. Results: Twenty-two trials were included [pharmacological (12), behavioural (5), physical (3), dietary (1)]. For TS and CTD, there was evidence for the intervention from four trials of z2-agonists (standardised mean difference 0.71; 95% CI: 0.18 to 1.23, p < 0.05; N = 1641) and two trials of atomoxetine (standardised mean difference 0.71; 95% CI: 0.18 to 1.23, p < 0.05; N = 1641). The evidence for stimulants, physical therapy, and dietary interventions was limited.
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 ARIPIPIRAZOLE 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
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
### 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 and 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 food intake
2. Concurrent presence of additional neuropsychiatric symptoms with similarly severe or moderate 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 Frequency
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 PANS patients respond to CBT at a similar rate to response seen in typical paediatric OCD
- No studies of SSRIs in PANS patients with OCD
- Tics - behavioural treatments effective, antipsychotics, medications no studies
- Systematic review examined range of treatments in PANS 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 structured diaries
- GAS exposure: throat swabs, serology for ASOT, anti-DNAse antibody titres
- Tic exacerbations defined as 6 points on YGTSS – TTS score; tic exacerbations 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.
Heyman, Liang, Hedderly
Archives of Diseases in Childhood 2021
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<tr>
<th><strong>CLASSIC TICS</strong></th>
<th><strong>FUNCTIONAL TICS</strong></th>
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<tr>
<td>Onset usually gradual, occurring at a young age and decreasing towards adulthood</td>
<td>A sudden and later onset</td>
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<tr>
<td>Tic severity often responds to medication / behavioural therapy</td>
<td>Often don’t respond to common drugs prescribed for classic tics</td>
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<tr>
<td>Rarely remit suddenly</td>
<td>Often remit suddenly</td>
</tr>
<tr>
<td>Wax and waning pattern</td>
<td>Associated with increased stress/recent events</td>
</tr>
<tr>
<td>Often runs in families</td>
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Tic attack vs Classic Tics (Demartini 2015, Ganos 2016)
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 movements, 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% diagnosis 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
GOSH Tic Disorders Service

- Paediatrician or CAMHS referral
- Differentiation tics/ functional tics and comorbidities
- Consultation & recommendations
- Group Psychoeducation
- Group ERP
- Limited neurodevelopmental assessment
Thank You & Questions