

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 February 8; 7(1): 1-66





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INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now indexed in PubMed, PubMed Central.

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NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

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E-mail: editorialoffice@wjnet.com
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Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
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PUBLICATION DATE
February 8, 2018

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<http://www.wjnet.com/bpg/gerinfo/204>

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Review of the evidence for the management of co-morbid Tic disorders in children and adolescents with attention deficit hyperactivity disorder

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Author contributions: Ogundele MO conceived the idea; Ogundele MO and Ayyash HA prepared the manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the authors who contributed their efforts in this manuscript.

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Manuscript source: Invited manuscript

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Received: October 27, 2017

Peer-review started: October 29, 2017

First decision: November 20, 2017

Revised: November 30, 2017

Accepted: December 5, 2017

Article in press: December 5, 2017

Published online: February 8, 2018

Abstract

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries. Tic disorders (TD) are common co-morbidities in paediatric ADHD patients with or without pharmacotherapy treatment. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. We carried out a literature review relating to the management of TDs in children and adolescents with ADHD through a comprehensive search of MEDLINE, EMBASE, CINAHL and Cochrane databases. No quantitative synthesis (meta-analysis) was deemed appropriate. Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and normal doses of psychostimulant use. Supratherapeutic doses of dextroamphetamine have been shown to exacerbate TD. Most tics are mild or moderate and respond to psychoeducation and behavioural management. Level A evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenalin inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics and comorbid ADHD. Priority should be given to the management of co-morbid Tourette's syndrome (TS) or severely disabling tics in children and adolescents with ADHD. Severe TDs may require antipsychotic treatment. Antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe Tics, but they only moderately control the co-occurring ADHD symptomatology. Short vignettes of different common clinical scenarios are presented to help clinicians determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TDs.

Key words: Tics disorders; Childhood; Attention deficit hyperactivity disorder; Adolescence; Tourette's syndrome

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Core tip: Attention deficit hyperactivity disorder (ADHD) and Tic disorders (TD) are common co-morbidities in children and adolescents, with 60% of children with Tourette's syndrome having ADHD. This review covers the classification, prevalence, aetiology, diagnosis and treatment of childhood TD and co-morbid ADHD. Most tics are mild or moderate, responding to psychoeducation and behavioural management. Level A evidence supports the use of alpha adrenergic agonists, Atomoxetine and stimulants for the treatment of Tics and co-morbid ADHD. Severe TDs may require antipsychotic treatment. Short clinical vignettes are presented to help guide the selection of the most appropriate treatment in each patient presenting with ADHD and co-morbid TDs.

Ogundele MO, Ayyash HF. Review of the evidence for the management of co-morbid Tic disorders in children and adolescents with attention deficit hyperactivity disorder. *World J Clin Pediatr* 2018; 7(1): 36-42 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/36.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.36>

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries^[1]. Up to 80% of ADHD patients have one or more co-morbid conditions which include Tic disorders (TD). There is a complex interplay between TD and ADHD in children and young people. TDs are common comorbidities in paediatric ADHD patients with or without treatment with pharmacotherapy. ADHD and other co-morbid disorders like Tics/Tourette's syndrome (TS), especially if left untreated, can have lasting impairing effects on several aspects of daily functioning.

Tics naturally wax and wane in clinical severity and are exacerbated by stress, including consequences of untreated ADHD. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. Some anecdotal evidence also suggests that tics may improve with ADHD treatment.

SYMPTOMS AND NATURAL HISTORY OF TD

Tics have been defined as sudden, rapid, recurrent, non-rhythmic, stereotyped, involuntary movements or vocalizations. Motor tic can be either simple or complex, depending on whether one or several muscle groups are simultaneously or concurrently affected. Motor tics commonly include behaviours such as eye-

blinking, lip-licking, or mouth opening. It can also involve more complex movements like facial grimacing, head movements, shoulder shrugging or combinations of these^[2].

Vocal or phonic tics are involuntary sounds that include throat clearing, coughing, barking, sniffing, unnecessary belching or more complex vocalizations such as repeating parts of words or phrases^[3].

TS (also known as Gilles de la Tourette's syndrome) is a complex neurodevelopmental disorder characterized by combination of motor and vocal tics. Motor tics often precede the onset of phonic tics of TS by many years. The phonic tics may commence from about the age of 3 years. Severe TS may manifest as forceful bouts of self-harming motor tics, including hitting or biting, as well as socially unacceptable utterances (coprolalia) and gestures^[3].

The Tourette's Syndrome Study Group definition from 1993 requires the concurrent presence of motor and vocal tics occurring almost daily for at least one year, beginning before the 21st birthday^[4]. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) requires both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently for the diagnosis of TS. It also describes TD/TS as waxing and waning in frequency and symptoms must have lasted for more than one year since the first onset^[5]. The average age of developing TS is 7 years, with a range from three to eight years. Most patients with childhood TD show remarkable symptoms improvement by the age of 19 years. Adult-onset cases of TS are usually the most severe forms of presentation^[3].

Motor or phonic tics often begin with the patient experiencing some psycho-sensory phenomena known as the "premonitory urge" which may be localized to an area of the tics or a generalised inner tension. Most individuals with Tics/TS also experience feelings of momentary relief after the tic has occurred. TD are typically exacerbated by stressful life-events associated with high levels of emotional excitements and fatigue, and can include normally routine activities such as the start of school, birthdays, arrival of a new sibling, changes in the social or physical environment like moving house or going on holidays.

The symptoms of childhood TD/TS are usually mild and they are almost invariably co-morbid with other mental health and behavioural problems including ADHD, Obsessive-compulsive behaviour or disorder (OCD), learning disabilities (LD) and mood disorders. Tics/TS can significantly impair the patient's self-esteem, peer and or family relationships^[3]. Although tics often improve after adolescence, recent studies suggest that comorbid OCD and ADHD often persist^[6]. Other common comorbidities in children with Tics/TS include anxiety disorders, depression, autistic spectrum disorder (ASD), conduct disorder (CD), oppositional defiant disorder (ODD), self-injurious behaviours, sleep disorders, rage attacks and personality disorders^[2,7].

CLASSIFICATION OF TD

DSM-5^[5] classifies TD into four categories, according to the duration and age of symptoms onset: (1) TS: Both multiple motor and one or more vocal tics (not necessarily concurrently) that have been present for more than a year; (2) Chronic TD: Presence of a single or multiple motor or vocal tics (not both), appearing before age 18, present for more than a year; (3) Transient TD: Single or multiple motor or vocal tics (not both), occurring nearly daily for at least 4 wk but not longer than 12 consecutive months; and (4) TD not otherwise specified: Tics that do not meet the conditions for definition of any other TD. This includes adult-onset tics.

PREVALENCE OF TD AND CO-MORBID CHILDHOOD ADHD

Transient TD affect between 5% and 25% of school children at any given time^[8]. The reported prevalence of TD/TS is variable according to different sample sources, definitions or diagnostic methods used. It is also influenced by the age and sex of the study cohorts. A published meta-analysis including 13 studies reported that the prevalence of childhood TS varied between 0.4% and 3.8% and average 1% among school children (higher in boys, 1.06% vs 0.25% in girls)^[9].

ADHD is the commonest neurodevelopmental comorbidity reported among children with TS. While only seven percent of children and adolescents with ADHD are diagnosed with TS, up to 60% of patients with TS have ADHD. ADHD diagnosis is generally known to antedate the occurrence of motor or vocal tics among children with TS, but their concurrent emergence is also possible^[2]. The Yale Global Tic Severity Scale (YGTSS) scores in children with ADHD are reported not to be significantly different from those without ADHD, but children with obsessive compulsive behaviours tend to have significantly higher YGTSS scores^[10].

AETIOLOGY OF TD

Several genetic studies among twins and families have contributed significantly to our knowledge about the important roles of genetic risk factors in predicting vertical transmission of TS and related TD. The exact nature and mechanism of the genetic inheritance are however unknown. The genetic vulnerability of TS has been associated with some extensively studied candidate genes, including the dopamine receptors (*DRD1*, *DRD2*, *DRD4*, and *DRD5*), the dopamine transporter, some noradrenergic genes (*ADRA2a*, *ADRA2C*, and *DBH*), and serotonergic genes (*5HTT*)^[3]. Abnormalities in any one or more of these genes could potentially act together with unfavourable environmental factors, to increase the risk of individuals having TD/TS.

POSSIBLE COMMON PATHOGENESIS OF CHILDHOOD TD AND ADHD

The risk for developing ADHD as well as TD is associated with early exposure to certain adverse perinatal conditions. The extensive co-occurrence of the two disorders also suggests a shared genetic background^[11,12]. Prenatal maternal smoking is associated with increased risk for TS/TD as well as its comorbidity with other psychiatric conditions^[13].

Abnormalities in noradrenergic and dopaminergic chemoreceptors and neurotransmission within corticostriatal circuits have been implicated in the development of both TS/Tics and ADHD. These alterations are thought to be responsible for clinical symptoms arising from failure to inhibit intrusive thoughts, sensory input, and motor output^[14]. Iron deficiency has also been commonly associated with ADHD and recently with Tics/TS^[15,16].

DIAGNOSTIC CHALLENGES OF TD

The Diagnostic and Statistical Manual, 5th edition (DSM-5)^[5] and the International Classification of Disease and related Health Problems, 10th revision (ICD-10)^[17] are the most universally accepted diagnostic criteria for TS/TD. The clinical nature and progression of TS/TD present the clinician with some peculiar challenges. The intermittent symptoms may delay recognition in the early stages of the disorder. Assessment of childhood and adolescent TD/TS requires multi-source feedback from several familiar carers to document the frequency and severity of the symptoms, specific triggers, and ascertain the level of any functional impairment, including effect on self-esteem and the associated mental health co-morbidities.

SCREENING AND ASSESSMENT TOOLS FOR TD

At least 5 severity scales have been recommended for use in children and young people with TS/Tics, including the Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression, Tourette's Disorder Scale, Shapiro Tourette Syndrome Severity Scale, and Premonitory Urges for Tics Scale. Six others have been suggested, including the Hopkins Motor and Vocal Tic Scale, Rush Video-Based Tic Rating Scale, Parent Tic Questionnaire and Tourette Syndrome Symptom List. The YGTSS is the commonest screening tool employed worldwide for both clinical and research purposes, and it is the most favoured tool recommended by TS international guidelines^[18].

A further two screening instruments in common use, have also been recommended by an International Movement Disorders Society subcommittee; Motor tic, Obsession and compulsions, Vocal tic Evaluation Survey

Table 1 Common differential diagnosis of Tics

Stereotypy (in developmental disorders such as autism spectrum disorders and stereotypic movement disorder)
Functional movement disorders in children
Neurological: Stroke, head trauma
Primary movement disorders: Dystonia
Post-infectious: PANDAS, Sydenham's chorea
Infectious: Encephalitis
Epileptic seizures
Toxic: Carbon monoxide poisoning
Chromosomal disorders: Down syndrome and Fragile X syndrome
Genetic conditions: Huntington's disease, Wilson's disease and Tuberous sclerosis
Medication-induced tics: Neuroleptics, Stimulants, Antiepileptics, Lithium

Modified from Oluwabusi *et al*^[19] 2016. PANDAS: Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

(MOVES) and Autism-Tics, Attention Deficit/Hyperactivity Disorder and Other Co-morbidities Inventory (A-TAC)^[18].

DIFFERENTIAL DIAGNOSIS OF TD

The diagnosis TS/TD is based on clinical history and examination, supplemented by various screening and diagnostic feedback tools. Both DSM-5^[5] and ICD-10^[17] preclude the presence of any direct physiologic causes such as a substance (*e.g.*, stimulants) or a general medical condition (*e.g.*, Huntington disease or post-viral encephalitis) to make a firm diagnosis of TS/TD. TS/TD need to be differentiated from any voluntary coordinated stereotyped movements or vocalisations, which may not always be easy to achieve clinically in younger children. TS/TD diagnosis must also exclude other specific dyskinetic disorders such as akathisia, tardive dyskinesia, or other hyperkinetic movement disorders (Table 1). Routine laboratory and radiological investigations may be required to exclude other organic causes of tics^[19]. Tics may be differentiated from other common movement disorders by its tendency to occur in a milder form during sleep^[3].

MANAGEMENT OF TICS/TOURETTE SYNDROME (ALONE OR CO-MORBID WITH ADHD)

Tics/TS are best managed in multidisciplinary teams with multifaceted expertise in Neurology, Psychiatry, Psychology, and Paediatrics, with supportive services from Education and Social welfare services. The primary choice of management strategies depends on the severity of the symptoms and their associated impairments.

Mild to moderate symptoms

First line of management for mild to moderate TD/TS involves comprehensive psychoeducation of patients and families, addressing the aetiology, triggering factors and management strategies of tics and associated behaviours, personal coping mechanisms, prognosis, and symptomatic natural progression^[14]. Counselling interventions for dealing with peer rejection, academic and family problems or employment difficulties are also recommended^[2].

Comprehensive Behavioural Intervention for Tics (CBIT) is a combination of several psychological support interventions including Psychoeducation, Functional analysis, Relaxation Training, Habit Reversal Therapy (HRT), social support and reward systems^[20]. Exposure and Response Prevention (ERP) is another type of therapy that enables the patient to effectively overcome and deal with the premonitory urges. For example, an alternative learnt movement is carried out for a brief moment after each pre-monitory feeling. These strategies are particularly helpful in older children^[2].

Growing evidence confirm effectiveness of various elements of the CBIT including self-monitoring (counting tics), relaxation techniques, and Habit reversal therapy involving awareness and competing response training^[21,22]. However, these comprehensive multidisciplinary support services are not readily available in many centres, mainly due to the paucity of well-trained therapists^[23]. These counselling and behavioural modification interventions may be sufficient to successfully manage many children with uncomplicated Tics/TS, who do not need Pharmacotherapy.

Moderate to severe Tics/TS symptoms

In more complicated cases causing interference with peer or family relationships, social interactions, academic or job performance, or with other functional activities, Pharmacotherapy for TD/TS may be recommended in addition to the first line counselling and behavioural interventions^[2].

First line pharmacotherapy

Alpha adrenergic agonists: Clonidine or Guanfacine (as single agent or combined with ADHD stimulants/non-stimulants) are the first line recommended treatment for tics/TS. These drugs were initially developed for the management of hypertension and have sedation or tiredness as major side effects. They can also cause possible rebound hypertension if stopped abruptly. There is a need to closely monitor blood pressure in patients on Clonidine or Guanfacine.

ADHD stimulants/non-stimulants: Apparent worsening or new onset of tics during ADHD treatment is oftentimes due to the coincidental waxing and waning

natural history of tics. It is best to persevere for a few weeks with normal doses of stimulant treatment (various formulations of Methylphenidate and or Dexamphetamines) if it is effectively controlling the ADHD symptoms. In most cases the tics will gradually subside spontaneously. If stimulants have to be stopped due to emerging or worsening tics, clinicians may consider re-challenging children with psychostimulants after a watchful period when the tics seem to have subsided. An alternative approach would involve treatment of ADHD and the co-morbid TD with alpha agonists either as replacement or additional therapy to psychostimulants.

Non-stimulant Atomoxetine should be considered as alternatives if alpha agonists are not tolerated. Atomoxetine can also be effective for treatment of ADHD with comorbid anxiety, and less effectively for co-morbid Tics/TS^[24].

Second line pharmacotherapy

Antipsychotics: Various generations of antipsychotics are the recommended second line management for more complicated cases of TS/Tics. Recent studies about the atypical antipsychotics such as Risperidone, and Aripiprazole, suggest that their efficacy in the control of severe TD/TS symptoms is related to their ability to selectively block dopamine D2 postsynaptic receptors. Reviews of the atypical psychotropics have shown demonstrable effective treatment for tics, but they do not affect premonitory urges, and they are only moderately effective in controlling the co-occurring ADHD symptomatology^[25].

The older generation of antipsychotics, such as Haloperidol and Pimozide, which were the preferred treatment options in the past due to their greater effectiveness, are now rarely used in the treatment of childhood TD/TS because of their significant adverse effects including extrapyramidal side-effects and tardive dyskinesia for Haloperidol, and cardiotoxicity for Pimozide^[26].

Adjuvant therapy

Deep brain stimulation (DBS) has recently become a viable therapeutic option for TS in refractory cases^[27]. A recent study suggests that iron deficiency may be associated with more severe tics and therapeutic iron supplements lead to alleviation of symptoms. The relationship between TD and iron deficiency appears to be independent of any co-morbidities such as OCD, ADHD, or anxiety^[15].

SUMMARY OF TREATMENT FOR ADHD AND CO-MORBID TD USING COMMON CLINICAL SCENARIOS

Clinical guidelines have been published for the management of TD in Europe^[28], Canada^[29], and the United States^[30]. We shall consider recommendations for ma-

nagement of ADHD co-morbid with TD/TS using three common clinical scenarios.

Scenario 1

In a patient with ADHD and co-morbid mild to moderate TD: Consider giving priority to the treatment of ADHD as it will likely be having the greater impact on the child's functioning and education. Furthermore, ADHD medications are more effective and have less potential side effects^[2]. Tics reduction (and not tics exacerbation) has been reported with acute immediate release Dexamethylphenidate (IR dMPH) challenge in children and adolescents with ADHD and co-morbid Tics disorder^[31]. However, supra-therapeutic doses of Dextroamphetamine should be avoided, as they may worsen tics severity in some individuals^[32].

Treatment of tics may be considered in these patients only if the symptoms are associated with significant functional impairments. Various clinical options for the management of the tics include temporary withdrawal of stimulant treatment, addition or replacement of the stimulants with alpha adrenergic agents (Clonidine or Guanfacine) and or non-stimulant Atomoxetine.

Scenario 2

In a patient with ADHD and co-morbid TS or severe tics: Greater benefit and satisfaction to the patient may be achieved by treating the Tourette's symptoms first^[2]. The treatment of TS/severe tics will follow the standard strategies of progressing from psychological and behavioural interventions to the first and or second line Pharmacotherapy, in that order. Treating the TS first offers the added advantage of minimizing the risk of worsening tics with the introduction of psychostimulants as the most effective treatment for ADHD.

Scenario 3

In a child already diagnosed with ADHD and treated with stimulants developing significant Tics disorder: New research evidence does not contraindicate continuing use of the stimulants. Conservative "watchful" approach may be adopted to check if the tics will abate spontaneously (following the natural course). In most cases the tics will gradually subside.

The next step would be to consider modification of treatment (add new drug or replace medication as in scenario 2). Studies have confirmed that combination of alpha 2 agonist like Clonidine with psychostimulant Methylphenidate is effective and safe for the management of ADHD and co-morbid TD^[2]. An earlier meta-analysis of 9 studies involving 477 subjects has confirmed that alpha-2 agonists offer the best combined improvement in both tics and ADHD symptoms. It also showed that Methylphenidate offers the greatest and most immediate improvement of ADHD symptoms without aggravating the tic symptoms. Atomoxetine and Desipramine also offer additional evidence-based treatments of ADHD in children with comorbid TD^[32].

CONCLUSION

Recent published evidence suggests that the incidence and severity of tics and TS are not increased by the use of psychostimulants, using the usual recommended dosing, except in a small number of individual cases. A more recent meta-analysis of 22 controlled trials among 2385 ADHD children has failed to demonstrate any significant relationship between treatment with stimulants and new tics or increasing severity of existing ones. Apparent symptom worsening or new tics appearing during ADHD treatment can often be attributed to the coincidental "waxing and waning" natural history of tics^[33].

Most tics respond to psychoeducation and behavioural management. Level A of evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenalin inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics/TS and comorbid ADHD^[14]. Priority should be given to the management of co-morbid TS or severely disabling tics in children and adolescents with ADHD.

Severe TD may require antipsychotic treatment (such as Aripiprazole or Risperidone). The newer atypical antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe tics, but they only moderately control the co-occurring ADHD symptomatology. Consideration of different common clinical scenarios could help to determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TD.

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P- Reviewer: Govindarajan GK, Wang YZ **S- Editor:** Ji FF
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