Published in final edited form as:
Pediatr Neurol. 2015 January ; 52(1): 25–35. doi:10.1016/j.pediatrneurol.2014.10.004.

Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND) and the TAND Checklist

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Abstract

BACKGROUND—Tuberous sclerosis complex is a multisystem genetic disorder with a range of physical manifestations that require evaluation, surveillance, and management. Individuals with tuberous sclerosis complex also have a range of behavioral, psychiatric, intellectual, academic, neuropsychologic, and psychosocial difficulties. These may represent the greatest burden of the disease. Around 90% of individuals with tuberous sclerosis complex will have some of these difficulties during their lifetime, yet only about 20% ever receive evaluation and treatment. The Neuropsychiatry Panel at the 2012 Tuberous Sclerosis Complex International Consensus Conference expressed concern about the significant "treatment gap" and about confusion

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We dedicate the TAND Checklist to the memory of Ann Hunt (1939–2014), who pioneered the systematic study of TAND in the 1980s and 1990s.

The 2012 International TSC Clinical Consensus Conference was organized by the Tuberous Sclerosis Alliance.

All authors listed (except L.L.) were members of the Neuropsychiatry Panel at the 2012 International TSC Clinical Consensus Conference under the chairmanship of P.J.d.V. L.L. contributed to the development of the TAND Checklist and performed pilot validation of the TAND Checklist.

Conflict of Interest Statement: None of the authors have any conflicts of interests related to the work in this article. V.H.W., L.L., A.W.B., K.C.E., and D.H. did not declare any potential conflicts of interest.

Supplementary data
A free-standing version of the TAND Checklist can be found at http://dx.doi.org/10.1016/j.pediatrneurol.2014.10.004.

regarding terminology relating to the biopsychosocial difficulties associated with tuberous sclerosis complex.

METHODS—The Tuberous Sclerosis Complex Neuropsychiatry Panel coined the term TAND—tuberous sclerosis complex-associated neuropsychiatric disorders—to bring together these multidimensional manifestations of the disorder, and recommended annual screening for TAND. In addition, the Panel agreed to develop a TAND Checklist as a guide for screening.

RESULTS—Here, we present an outline of the conceptualization of TAND, rationale for the structure of the TAND Checklist, and include the full US English version of the TAND Checklist.

CONCLUSION—We hope that the unified term TAND and the TAND Checklist will raise awareness of the importance of tuberous sclerosis complex-associated neuropsychiatric disorders and of the major burden of disease associated with it, provide a shared language and a simple tool to describe and evaluate the different levels of TAND, alert clinical teams and families or individuals of the importance of screening, assessment, and treatment of TAND, and provide a shared framework for future studies of tuberous sclerosis complex-associated neuropsychiatric disorders.

Keywords

behavior; psychiatric disorders; autism; mental health; neurocognition; learning disorders; neuropsychological; psycho-social

Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder associated with multiorgan involvement, including the brain, kidneys, heart, eyes, and lung.[1,2] The disorder has a birth incidence of approximately 1:6000 and is seen at similar prevalence rates around the globe.[3] In approximately 85% of cases, a mutation is identified in the *TSC1* (chromosome 9q34) or *TSC2* (chromosome 16p13.3) genes. The TSC1–TSC2 protein complex acts as an upstream regulator of mammalian target of rapamycin (mTOR).[1,2,4] Disruption of this regulatory role leads to mTOR over-activation and to dysregulated growth control, thus explaining the fundamental pathophysiological mechanism of the disorder.[1,2,4] In recent years, molecularly targeted treatments using mTOR inhibitors have been introduced for some of the specific organ systems involved, such as subependymal giant cell astrocytomas of the brain and angiomyolipomas of the kidney.[5–8]

Given the significant progress in understanding the pathophysiology of TSC over the last 2 decades, the International Consensus Conference was convened in 2012 to revise the diagnostic criteria and to refine the assessment, surveillance, and treatment guidelines for TSC. Revised diagnostic and surveillance guidelines were published in 2013.[9,10]

Apart from the range of physical manifestations of TSC, individuals with the disorder may also be affected by a wide array of behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties.[11,12] In both clinical practice and scientific publications, these multiple levels of difficulties have been referred to by many different terms, including "neurocognitive issues," "neurobehavioral difficulties," "learning issues," "mental health issues," "neuropsychiatric disorders," "cognitive and behavioral difficulties," and so on. Most individuals who live with TSC will experience some of these difficulties in their lifetime. Similar to the physical manifestations of TSC, there is also growing evidence that specific elements of neuropsychiatric disorders in TSC may be directly attributable to dysregulation of mTOR signaling and that mTOR inhibitors might therefore also become molecularly targeted treatments for some of these aspects of TSC.[11–15]

In 2003 an international consensus panel was convened to develop guidelines for the assessment of "cognitive and behavioral problems" in individuals with TSC. The recommendations were published in 2005.[16] The panel made two main recommendations. The first was to perform regular assessment of cognitive development and behavior in all children and adolescents with TSC to establish a baseline for evaluating changes in developmental trajectories and to identify and treat emerging difficulties. The second was to perform a comprehensive assessment (particularly a comprehensive physical evaluation) in response to sudden or unexpected *changes* in cognitive development or behavior to identify and treat the underlying cause of neurobehavioral change.[16]

In a survey of members of the UK Tuberous Sclerosis Association 5 years after the publication of these guidelines, only 18% of all families had ever received any of the evaluations or treatments recommended in the 2005 guidelines. Given that more than 90% of all individuals with TSC are likely to have some of these challenges,[17] the "treatment gap" (the difference between clinical need and services provided) was therefore in excess of 70%. This finding is in keeping with global findings of treatment gaps in mental health where it is not uncommon for 70%–80% of individuals who have mental disorders not to receive any treatment.[18]

Given the multidimensional nature of these difficulties associated with TSC across multiple levels, the clinical and scientific confusion about different terminologies used, and the significant treatment gaps identified, the Neuropsychiatry Panel at the 2012 International Consensus Conference were keen to identify a strategy that would increase awareness of the need to screen for these difficulties, simplify and clarify the terminology used around behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial aspects of TSC, and develop a simple tool to facilitate clinical teams and families to screen for these challenges to identify areas that require more in-depth evaluation or treatment.

The Neuropsychiatry Panel commented that the "treatment gaps" observed in TSC were similar to those observed in the human immunodeficiency virus (HIV) community, where there used to be an overemphasis on physical treatment of HIV-positive individuals without consideration of the major neurocognitive and neuropsychiatric features of HIV.[19] The HIV community introduced the concept of HAND (HIV-associated neurocognitive disorders) as a strategy to raise awareness of such concerns. Inspired by the HIV example, the TSC Neuropsychiatry Panel therefore decided to coin the term TAND (TSC-associated neuropsychiatric disorders) and recommended that all individuals with TSC should be screened for TAND at least once per year. To facilitate the process, a TAND Checklist was developed. Pilot validation of the TAND Checklist was performed and is presented elsewhere.[17]

Here, we outline the conceptualization of the multidimensional nature of TAND and present a TAND Checklist for clinical use.

The multiple dimensions of TAND

Infants, children, adolescents, and adults with TSC may present with a varied and variable range of challenges across multiple "levels or dimensions."[11,20]

Behavioral level

This level refers to any observed behaviors that may cause concern to the individual with TSC, their parents, caregiver, or professionals. High frequency behavioral presentations in TSC include anxiety, depressed mood, aggressive behaviors, temper tantrums, attention-related behaviors (such as difficulty concentrating, hyperactivity, impulsivity), social, and communication-related behaviors (such as speech and language delays, poor eye contact, difficulties in relationships with peers, repetitive behaviors), self-injurious behaviors, and eating or sleep difficulties.[11,20–22]

These behavioral concerns are typically identified through self-report, parental or caregiver report, or are observed by teachers or other professionals who work with an individual with TSC. A range of rating scales can be used to quantify the behavioral level. However, rating scales typically have limited age ranges and tend not to be used across the ability spectrum (i.e., in both those with and those without intellectual disability). These rating scales are sometimes used to identify people "at risk" for diagnosable psychiatric disorders. On their own, behavioral concerns do not constitute psychiatric disorders, given that many factors need to be considered to determine the appropriateness or inappropriateness and reasons for such concerns. For instance, a 2 year old with temper tantrums would be considered to have developmentally appropriate behaviors that require basic parenting management; in contrast, a 15 year old who still displays significant temper tantrums may require additional evaluation to understand the reasons and triggers for such behavior.

The behavioral level often represents the "reasons for referral" for a next-step evaluation by a primary care or specialist team.

Psychiatric level

At this level, behaviors of concern are examined and evaluated in the context of the individual's overall developmental level and in terms of their biological, psychological, and social profile. This is often referred to as a biopsychosocial formulation.[11] Where an individual has sufficient behavioral features of specified intensity and duration that cause distress or impairment to the individual, they may meet criteria for a psychiatric disorder, as defined by diagnostic systems such as the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5), or the International Classification of Diseases, tenth edition.[23,24]

The most common psychiatric disorders observed in association with TSC include neurodevelopmental disorders such as autism spectrum disorders (25%–50%) and attention deficit hyperactivity disorder (ADHD, 30%–50%), as well as depressive and anxiety disorders (30%–60%).[11,12,20,25–28] Some of the clear advantages of identifying and diagnosing psychiatric disorders include the ability to provide appropriate psycho-education and treatment and to support families to find the appropriate educational environment for a child who might have a neurodevelopmental disorder.

Intellectual level

At this level, we describe the intellectual developmental abilities of an individual to identify their overall functional and adaptive behaviors in comparison with others of the same chronological age. In DSM-5 and the International Classification of Diseases, eleventh edition (to be released in 2015), the intellectual level is defined by the combination of formal measures of intellectual ability (such as IQ-type tests) and evaluation of adaptive behaviors (such as self-care, daily living skills, communication, and social abilities in daily life).[23,24] In the general population, about 98% of individuals fall within or above the normal range of intellectual ability along a normal distribution pattern, and about 2% fall in the intellectual disability range, that is, below two standard deviations of the mean IQ or IQ <70.

In TSC, approximately 50% of individuals have an IQ score of less than 70 and therefore have intellectual disability, ranging from mild or moderate to profoundly impaired.[29] Population-based studies have identified that as many as 30% of individuals with TSC fall in the profoundly impaired range.[29,30] Given these findings, it is therefore very important to consider the overall intellectual level of each individual with TSC, to determine their likely support needs in daily life, to consider appropriate educational support required and to consider the behavioral problems presented. For instance, a child who presents with significant overactivity and inability to concentrate who also has significant intellectual disability may be judged to have overactivity and concentration difficulties in the context of his or her intellectual developmental level, rather than requiring an additional psychiatric diagnosis. It is well established that individuals with intellectual disability have a 4–5-fold increase in the rates of psychiatric disorders across the life span,[31] and this is also the case in TSC.[11,21]

Academic level

At this level, we describe the specific learning disorders associated with school performance, such as reading, writing, mathematics, and spelling. About 30% of school-aged children with TSC who have entirely normal intellectual ability, present with specific academic difficulties that require evaluation and support.[11] Many children with TSC, particularly those with above-average and superior intellectual abilities, are often not considered for an individual education plan (or equivalent program of educational support) even if they have specific academic difficulties. Given the apparent intellectual ability of the child (at the intellectual level), children are often interpreted as being “lazy,” “unwilling,” or “stubborn” in a school setting, and educational systems do not consider and look for specific learning disorders. For these reasons, the academic level needs to be considered as a distinct level of enquiry.

Neuropsychological level

Neuropsychological evaluations are used to describe the strengths and weaknesses of brain referenced systems used for learning, thinking, and behavior regulation. These include executive skills (such as planning, working memory, perspective taking), attentional skills (such as selective attention, sustained attention, dual tasking), language skills (including receptive and expressive language, grammatical and pragmatic use of language), memory skills (such as recognition and recall), and visuospatial skills (such as spatial navigation, drawing, constructional skills). These investigations are typically performed by clinical psychologists or neuropsychologists with relevant training in formal evaluation and interpretation, using a wide range of standardized measurement tools.

The neuropsychological level has a clear correlation with many behavioral concerns, with psychiatric disorders and with intellectual or academic ability. However, individuals with TSC may also have very specific neuropsychological deficits (typically defined as performance less than the fifth percentile on a measure). For instance, specific deficits in working memory, cognitive flexibility, or dual tasking may occur[32,33] and might correlate with behavioral challenges in real life.[34]

Psychosocial level

At this level we consider important determinants of quality of life, such as self-esteem, family functioning, parental stress, and relationship difficulties. All these are markers of resilience and burden of care, and all the psychosocial factors may be amenable to intervention and support. There are very high rates of psychosocial difficulties in TSC.[11,35] However, it is rare for families and individuals who live with TSC to be asked by clinical teams about their psychosocial functioning despite the core importance of this level.

The concept of TAND

TAND aims to bring together under a single term the multiple levels of involvement that relate to the neurobiological, psychological, and social aspects of TSC. The term was coined to generate a unifying rubric to be used as a “short-hand” to capture all the possible functional manifestations, complications, and consequences of TSC that relate to behavior, mental health or psychiatric disorders, neurodevelopment, intellectual, academic, neuropsychologic, and psychosocial abilities.

The term is not, however, meant to imply that all the levels are similar. In fact, TAND represents an umbrella term under which each of the possible levels of involvement should be considered, classified, evaluated, and treated. The hope is that use of the term TAND will immediately indicate to the user and listener the overall “field” of interest and that the levels or “domains” under the umbrella term can then be discussed with an improved, shared language.

Given the variability of TAND manifestations, it seems each individual with TSC may have their own unique TAND profile that will require a personalized evaluation and management plan. This TAND profile may of course also change over time, thus supporting the need for re-evaluation on a regular basis. A small proportion of individuals with TSC may never have

TAND problems. However, it is also important to remember that TAND may arise later in life after many years of apparently “normal” functioning.

The TAND Checklist

Given the attempt of the Neuropsychiatry Panel to unify terminology and delineate a shared language to describe the multiple dimensions of TAND, we agreed to develop a short, freely accessible TAND Checklist to aid health-care professionals and families in screening for TAND.

The purpose of the TAND Checklist is to act as a memory aid or a basic structure to guide a conversation between the clinician and family or individual with TSC. The conversation that flows from the TAND Checklist should give a sufficient structure to the team to generate a priority list and action plan for next steps. Some of these actions may include basic psycho-education and provision of information; others may require referral for specialist evaluation or treatment.

The TAND Checklist is not a questionnaire or rating scale where a set “threshold” needs to be crossed to indicate clinical need or a likely clinical diagnosis. Any of the items on the TAND Checklist may be sufficient to lead to an action plan agreed between clinical team and family or individual with TSC. For instance, a conversation using the TAND Checklist that identifies a child to have significant and persistent sleep difficulties should be sufficient to lead to further evaluation to identify the underlying causes of these difficulties. Where use of the TAND Checklist identifies a child as having specific academic difficulties in reading or mathematics but where an individual educational plan has not been considered, this should lead to conversations with the appropriate educational authorities.

The overarching aim of the TAND Checklist is therefore to provide a simple framework for a conversation about TAND. The hope is that the TAND Checklist will provide a systematic approach to a potentially bewildering array of difficulties, provide a shared language to talk with families about and troubleshoot needs and next steps, and facilitate next-step evaluation or treatment for TAND.

The structure of the TAND Checklist

The overall structure of the TAND Checklist is outlined in the Table. Conceptually, the 12 items (referred to as questions) follow the levels of investigation outlined previously and require simple YES or NO responses to most questions.

The introductory items (questions 1 and 2) aim to get a general sense of developmental milestones and of the current level of functioning of the individual about whom the conversation is taking place. These items were placed first to ensure that the interviewer has a sense of the functional abilities of the individual before they start talking about the behavioral items. For instance, it is helpful to know if someone has no expressive language (question 1d, 1e, 2a) before asking about repeating words and phrases over and over (question 3i).

The behavioral items section (question 3) lists the high frequency behaviors of concern in TSC. The psychiatric diagnoses that are most commonly seen in association with TSC are listed next (question 4). These include autism spectrum disorder, ADHD, anxiety disorders, and depressive disorders. It is not clear from the TSC literature how common obsessive compulsive disorders (OCDs) are in TSC. In clinical practice, many children with TSC referred for possible OCD meet criteria for autism spectrum disorders rather than OCD. For this reason, the item was included. Psychotic disorders do not appear to be over-represented in TSC,[11,27,28] and most psychotic phenomena seen in a clinical setting are more likely to be associated with seizure disorders, particularly temporal lobe discharges.[11,36] For this reason, psychotic disorders were listed.

Intellectual disability (question 5) is explored in terms of previous formal assessments and in terms of parental, caregiver or self-perception of intellectual ability. The reason for this was two-fold. First, many people with TSC never receive formal assessments of IQ. Second, there may be a discrepancy between “measured” intelligence and “perceived” intelligence. It is important to consider any discrepancies between these two. It is also very common for individuals with TSC to have a very uneven profile of intellectual strengths and weaknesses, with some having stronger verbal than perceptual skills (or vice versa) and others having a very different profile.

The item on academic abilities emphasizes the standard scholastic skills or learning disorders associated with reading, writing, mathematics, or spelling but should be an opportunity to ask about any school-based or school-related difficulties (question 6). The emphasis in item 7 on neuropsychologic skills is on those neuropsychologic deficits most commonly reported in association with TSC to date, including deficits in memory recall, attentional skills, dual tasking, visuospatial, and executive skills.

Item 8 focuses on core aspects of psychosocial functioning including self-esteem, parental stress, and family relationships. This item may also provide an opportunity to ask about other psychosocial aspects, as required.

Items 9 and 12 are short measures of impact. In item 9, the respondent is asked for their view of the overall impact of TAND; in item 12, the health-care professional documents their judgment of the overall impact of TAND. Discrepancies between parent or family and health-care professional ratings of impact should lead to a reflection on the possible reasons for such a difference. The difference may relate to over- or under-reporting on the part of the family or individual, and could provide some indication of family resilience in cases where the impact is rated as relatively low, in spite of significant TAND challenges.

Items 10 and 11 were included for clinical purposes to help clinician and family to prioritize areas for next steps and to provide families or individuals with the opportunity to identify concerns that may not have been listed in the TAND Checklist.

The full TAND Checklist is presented in the Figure and is available as a supplement for download (Supplementary data).

Pilot validation of the TAND Checklist

The pilot validation of the TAND Checklist, using a mixed-method approach, is presented in detail elsewhere.[17] In phase I of the pilot validation, expert professionals (n = 20) and expert parents or caregivers (n = 42) from 28 countries were asked to comment on the clarity, comprehensiveness, ease of use, and likely use of the TAND Checklist. Results suggested that the TAND Checklist was clear, comprehensive, and easy to use. Participants generally felt that clinical teams would use it, but that families and caregivers may need to drive use. Feedback from participants led to refinements of the TAND Checklist. In Phase II of the pilot validation, the TAND Checklist was administered to 20 families in Cape Town, South Africa, who were also asked to complete four widely used and validated rating scale measures of general mental health symptoms (the Strengths and Difficulties Questionnaire), autism-related behaviors (the Social-Communication Questionnaire), disability (the Wessex Rating Scale), and executive functions (the Behavior Rating Inventory of Executive Functions).[37–40] The TAND Checklist showed very good-to-excellent internal consistency, and strong correlations with external validation tools, thus suggesting good external validity.[17] Families also rated the TAND Checklist as clear, understandable, comprehensive, and easy to use. Overall pilot validation suggested that the TAND Checklist would provide a useful screening tool in clinical settings.

A very striking observation from the pilot validation data was that 100% of participants had one or more lifetime reported TAND behavioral difficulties, 97% had two or more difficulties, 93% had four or more difficulties, and 89% had six or more behavioral difficulties.[17]

How does the TAND Checklist fit into the 2012 International TSC consensus recommendations for the assessment and management of TAND?

As outlined elsewhere,[10] the Neuropsychiatry Panel recommended screening for TAND at least annually. We suggest that the TAND Checklist might be a useful guide to perform this task. Any areas of concern identified should lead to appropriate next-step evaluations or treatment.

In addition, we also recommended that comprehensive formal assessments for TAND should be performed at key developmental time points. These include infancy (age 0–3), pre-school years (age 3–6), primary school years (age 6–9), adolescence (age 12–16), early adulthood (age 18–25), and as required thereafter. Management strategies should be based on the TAND profile of each patient and should be based on evidence-based good practice guidelines or practice parameters for individual disorders (e.g., autism spectrum disorder, ADHD, anxiety disorder). Health-care professionals and educational teams should always consider the need for an individual educational plan. As recommended in the 2005 guidelines, sudden change in behavior should always prompt medical or clinical evaluation to identify any potential treatable medical causes (e.g., SEGA, seizures, renal disease).[16]

Next steps with the TAND Checklist

The TAND Checklist is provided here in English. Next steps will include working with local organizations in various countries to prepare translations of the TAND Checklist. Translations will be done using a standardized procedure including translation, blind back-translation, and authorization by the authors of the TAND Checklist. The TAND Checklist was developed to be freely available to increase the likelihood of its uptake in real-life settings.

Further studies using the current version of the TAND Checklist will be able to establish other aspects of the psychometric properties of the tool and can use the TAND Checklist as an instrument to document TAND behaviors in a simple, but systematic and consistent way.

Conclusion

Here the Neuropsychiatry Panel of the 2012 International Consensus Conference for TSC presented the rationale for and conceptualization of a new term, TAND. The overall purpose of this new term was to define a unifying construct to describe the multidimensional biopsychosocial manifestations seen in TSC. We hope that this unified term will raise awareness of the importance of TAND and of the major burden of disease associated with it, provide a shared language to describe and evaluate the different levels of TAND, alert clinical teams, families and individuals of the importance of screening, assessment, and treatment of TAND, and provide a shared framework for future studies of TAND.

The TAND Checklist was developed to provide a simple, easy-to-use, and relatively quick aide memoire for clinical teams and families. In essence, it was developed to be a framework for a conversation between health-care professionals and families about this important but under-investigated yet fundamental domain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The conference was supported by sponsors of the Tuberous Sclerosis Alliance without playing a role in the planning or having a presence at the conference and the resulting recommendations: the Rothberg Institute for Childhood Diseases, Novartis Pharmaceuticals, Sandra and Brian O'Brien, and Questcor Pharmaceuticals. P.J.d.V. receives support from NRF, PERC and the Struengmann Fund. M.S. receives support from the NIH 1U01NS082320-01.

P.J.d.V. and M.S. have received funding from Novartis for investigator-initiated clinical trials unrelated to this study and P.J.d.V., M.S. and A.J. have received honoraria as advisory board members for Novartis on other projects. P.J.d.V. was also a study steering committee member on three Novartis-sponsored clinical trials. D.D. has received financial support from Eli Lilly and Company for work unrelated to this study. B.H.K. has received financial support from Roche for work unrelated to this study.

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TABLE

Structure of the TAND Checklist

Item	Level of Investigation
Question 1	Basic developmental milestones
Question 2	Current level of functioning
Question 3	Behavioral concerns
Question 4	Psychiatric disorders diagnosed
Question 5	Intellectual ability
Question 6	Academic skills
Question 7	Neuropsychological skills
Question 8	Psychosocial functioning
Question 9	Parent, caregiver, or self-rating of the impact of TAND
Question 10	Prioritizing list
Question 11	Additional concerns
Question 12	Health-care professional rating of the impact of TAND

Abbreviation:
TAND = Tuberous sclerosis complex-associated neuropsychiatric disorders