

# TAND: Medication

November 8, 2021



# Reminder of Recording

The webinar is being recorded. By participating in this webinar, you have consented to the recording and future distribution. The camera setting by default has been turned off for all participants. We encourage you to participate on camera if you feel comfortable doing so, but if you do not wish to be on the recording, please keep your camera off throughout the presentation.

# Thank You to Our Sponsors

Presenting Sponsor



National Support Sponsors





## **Today's Presenter:**

David W. Dunn, MD, the Arthur B. Richter Professor of Child Psychiatry and Professor of Psychiatry and Neurology at Indiana University School of Medicine

# TAND: Role of Medications

TSC-associated Neuropsychiatric Disorders: TAND

David W. Dunn, MD    Nov 2021

# Disclosures

---

- Professor of Psychiatry and Neurology, Indiana University School of Medicine
- Consultant, speaker bureau: Nobelpharma
- Stocks: none
- Travel: American Board of Psychiatry and Neurology
- TS Alliance: Scientific Advisory Board

# Goals and Objectives

---

- Goal: provide a clinically practical update on the pharmacological treatment of TAND
- Objectives: Participants should be aware
  - a) of manifestations of TAND
  - b) of medications that may be beneficial in treatment of TAND
  - c) of potential adverse effects of medical interventions

# TAND

---

- Behavioral level
- Psychiatric level
- Intellectual level
- Academic/scholastic level
- Neuropsychological level

de Vries et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. *Pediatric Neurology* 2015; 52: 25-35



# TAND: Behavioral level

- Overactivity 45%
- Sleep difficulties 44%
- Impulsivity 43%
- Anxiety 33%
- Mood swings 30%
- Severe aggression 24%
- Depressed mood 19%

de Vries Orphanet J Rare Diseases 2018; 13: 157

# TAND: Psychiatric Diagnosis

- Autism spectrum disorder: 21%
- ADHD: 29%
- Anxiety disorder: 10%
- Depression 6%

de Vries 2018

# Psychiatric Problems in TSC

Smalley, Burger, Smith J Med Genet 1994; 31: 761-765

	TSC+	TSC-
Mood disorder	35.3%	6.2%
Substance abuse	5.9%	0
Anxiety disorder	58.8%	12.5%
ADHD	13.3%	6.7%
Any psych dis.	76.5%	25.0%

# TAND: intellectual and academic levels

- Normal IQ: 44%
- Mild ID: 28%
- Moderate ID: 15%
- Severe or profound ID: 12%
- Learning disability: 58.6%
- Additional problems: school refusal, anxiety about school, low self-esteem

# Problems with Attention in TSC

- 20 children with TSC and 17 sibling controls
- 18/20 children with TSC deficits on at least one attentional task, significant differences in 7/8 variables after controlling for IQ
- Problems with attention not predicted by seizures, AEDs, or parent report of ADHD-like symptoms

de Vries et al. Am J Med Genet 2009; 149A: 387-395

# Health burden and quality of life

- Most bothersome TSC manifestations:  
Pediatric-seizures-32%, cognition-25%,  
skin-15%  
Adults-skin-15%, sleep-10%, kidney-9%
- Quality of life (adults with TSC): worse than cancer patients for social function, emotional and mental health, better for general health, vitality

Rentz et al. Pediatric Neurology 2015; 52: 435-441.

# Caregivers Impact

- Lower physical and mental health quality of life than US-based norms for healthy adults
- Depression: mild to severe range scores on Hamilton Depression Inventory in 42% of TSC caregivers
- Depression: 19.3% of TSC caregivers on psychotropic medications (national average 11.1%)

Rentz et al. J Child Neurol 2015; 30: 1574

# Defining the Problem and Starting Treatment

- Pediatrician or family doctor
- Psychologist for testing and counseling
- Child neurologist, developmental pediatrician, or child and adolescent psychiatrist for medication management
- Comprehensive tuberous sclerosis clinic



# Problems More Likely with TSC

---

- , Intellectual disability
- Epilepsy
- Polypharmacy
- Multiple manifestations of TSC

# Antiseizure Drugs: adverse effects

---

- Aggression: potential adverse effects for most AEDs, especially perampanel, topiramate, levetiracetam, clobazam
- Impaired attention: barbiturates, valproate, lacosamide, topiramate, zonisamide

# Seizure Risk for Psychotropic Drugs

(Alper et al. Biol Psychiatry 2007)

Drug	Standardized Incidence ratio
Clozapine	9.50
Olanzapine	2.50
Quetiapine	2.05
Other antipsychotics	1.03
Bupropion IR	1.58
All other antidepressants	0.31
clomipramine	4.08

# Pharmacogenomics

---

- Study of how genetic variations affect response to medications
- Pharmacokinetic: cytochrome P450 system, genes involved in drug metabolism
- Pharmacodynamic: genes affecting neuronal function

# Autism Spectrum Disorder

Aggression, irritability, anxiety, and sleep disruption

# Assessment for Challenging Behavior

---

- Physical illnesses: pain, dental problems, constipation, seizures
- Medications: new medication or change in dose
- Environmental changes: home, school, day care, residential placement
- Behavioral disorders

# Autism: Behavioral Treatment

---

- Education for family
- Genetic counseling: recurrence risk of 5-6%, behavioral or cognitive symptoms in 20%
- Early intervention for child
- Teach functional skills in speech and social adaptation
- Psychological treating using applied behavioral analysis (ABA), deliver in naturalistic context to promote generalization
- Limited data for OT sensory integration therapy

# Behavior Modification for Autism or Mentally Handicap

---

- Watch for and anticipate antecedents
- Reward positive behaviors: primary-activities, stimulation; social-attention, praise
- Reduce negative behaviors: ignoring, time-outs



# Autism: psychopharmacology

---

- Use in conjunction with education and behavioral therapy
- Identify target symptoms
  1. Irritability, aggression
  2. Hyperactivity, impulsiveness, inattention
  3. Repetitive behaviors, anxiety, or depression
  4. Sleep disturbance
- If possible, use monotherapy and drugs proven effective in double-blind, placebo-controlled trials

# ASD: pharmacology-levels of evidence

---

- Good evidence, RCT: Antipsychotics-haloperidol, risperidone, aripiprazole (Abilify)
- Fair evidence: Medicines for ADHD-methylphenidate, guanfacine, atomoxetine (Strattera)
- Minimal evidence or conflicting: Antidepressants-fluoxetine, citalopram (adults not children), buspirone; valproic acid, olanzapine, amantadine, naltrexone

# Aggression

---

- Assess for medical and environmental triggers
- Assess for associated psychiatric conditions: ADHD and disruptive behavior disorders, autism spectrum disorders, mood disorders, anxiety, psychosis
- Start with behavioral therapy
- Use psychopharmacology based on associated condition

# Aggression: psychopharmacology

---

- Stimulants, particularly methylphenidate, are effective, both in ADHD and in disruptive behavior disorder without ADHD
- Severe aggression in children: combined treatment with parent training and stimulant plus risperidone (average dose 1.65 mg/day) had moderate improvement compared to placebo (Aman et al. JAACAP 2015 and Barterian et al JAACAP 2017)

# Autism and TSC: irritability, aggression, and hyperactivity

---

- Assess for environmental triggers
- Assess for comorbid depression or anxiety
- FDA approved: risperidone and aripiprazole for severe aggression or irritability
- Possible options: guanfacine or clonidine for mild irritability; haloperidol, olanzapine, paliperidone, or valproate as back up options; clozapine after multiple drug failures

# Side Effects of Atypical Antipsychotics

- Weight gain
- Metabolic syndrome
- Elevated prolactin
- Prolongation of QTc interval
- EPS
- others

# Weight gain

---

- Highest risk: clozapine, olanzapine
- Moderate risk: risperidone, quetiapine
- Minimal risk: ziprasidone, aripiprazole

Diabetes Care 2004;27:596-601

# ASD and anxiety or repetitive behaviors

---

- Start with fluoxetine, probably effective; case series possible efficacy with fluvoxamine, sertraline, and buspirone
- Some reduction in repetitive behaviors with risperidone and aripiprazole alone or combined with SSRI



# ASD and sleep disruption

---

- Children with ASD have disrupted sleep: delayed sleep onset, nocturnal arousals, and early morning awakenings
- Asses with polysomnography
- Abnormal circadian secretion of melatonin
- Treatment options: melatonin, maybe alpha adrenergic, doxepin, gabapentin, trazodone, nonbenzodiazepine

# ADHD

ADHD alone and with Autism

# ASD and ADHD

- Stimulants: 49% of children improvement with methylphenidate, 18% discontinued due to adverse effects (RUPP 2005)
- Guanfacine ER: Hyperactivity decreased in 44% versus 13% on placebo (Shahill et al. 2015)
- Atomoxetine: 21% much improved vs. 9% on placebo, continued improvement in open label trial (Harfterkamp et al. 2013)
- Other options: RSP, aripiprazole, clonidine, or polypharmacy

# Positive effects of ADHD medications

- Better grades and increase rate of graduation
- Improved quality of life
- Reduced risk of injuries
- Reduced arrest for crime
- Improved response inhibition and sustained attention, not working memory

# Stimulant Medications

	Methylphenidate	Amphetamine
Short (4 hr) acting	Ritalin, Methylin, Focalin	Dextroamphetamine, Evekeo, Zenzedi
Intermediate (8 hr)	Ritalin LA, Metadate CD	Adderall, Dexedrine spansule
Long (12 hr) acting	Concerta, Focalin XR, Daytrana, Quillivant, QuilliChew, Aptensio XR, Cotempla XR-ODT, Adhansia, Jornay PM	Adderall XR, Vyvanse, Adzenys XR-ODT, Dyanavel XR, Mydayis

# Adverse effects

- Most common: headache, stomachache, decreased appetite, insomnia
- Preschool age children: irritable dysphoria
- Less common: increased heart rate, increased blood pressure, tics, skin picking and nail biting, reduced growth rate
- Rare: hallucinations, mania

# Non-stimulants: atomoxetine, clonidine, guanfacine

---

- Advantages:

Less negative effect on appetite and sleep

Helps with tics, anxiety, and depression

- Disadvantages

Lower effect size 0.5-0.7

Slower to take effect (2-3 weeks)

Adverse effects

# ADHD and Epilepsy: treatment

- ADHD medication does not increase the risk of seizures Wiggs et al. Neurology 2018; 90: e1104-e1110; Auvin et al. Epilepsia 2018; 59: 1867-1880
- Methylphenidate does not lower the seizure threshold Downs et al. Expert Rev Neurotherapeutics 2017
- Less data but amphetamines and atomoxetine probably effective and safe



# Anxiety and Depression

# Anxiety and Depression: clinical presentations

- Pre-school age:
  - Anxiety: oppositional, somatic
  - Depression: anxiety, somatic
- School age:
  - Anxiety: misinterpretation of social cues
  - Depression: decreased self-esteem, withdrawal, school trouble

# Clinical presentations: Adolescents

---

- Anxiety: social anxiety, panic attacks
- Depression: school problems-cognitive difficulties, sleep disruptions, change in appetite

# Anxiety and Depression: What Works

---

- Generalized (GAD), separation, and social anxiety disorders: SSRIs first line if medication needed
- OCD: CBT or combined CBT+SSRI, second line clomipramine, third polypharmacy
- Depression: CBT, SSRI, or combined CBT+SSRI

# Antidepressants

	Initial dose	Usual dose	Maximum dose
Fluoxetine (Prozac)	10 mg	20-40 mg	60 mg
Sertraline (Zoloft)	12.5-25 mg	50-150 mg	200 mg
Citalopram (Celexa)	10 mg	20-40 mg	40 mg
Escitalopram (Lexapro)	5 mg	10-20 mg	20 mg
Fluvoxamine (Luvox)	25 mg	100-300 mg	200-300 mg
Venlafaxine (Effexor)	37.5 mg	150-225 mg	300 mg
Duloxetine (Cymbalta)	20 mg	40-60 mg	60 mg
Bupropion (Wellbutrin)	100 mg	300 mg	400-450 mg

# SSRIs: side effects

---

- Akathisia
- GI: cramps, diarrhea, nausea, vomiting
- Weight gain: maximal with sertraline
- Aggression [odds ratio 2.79 (1.62-4.81)]
- Sexual dysfunction
- Myoclonus
- Insomnia

# SNRI side effects

- Same as SSRI side effects plus extras
- Increased blood pressure and heart rate
- Jitteriness
- Dry mouth
- Sweating
- Dizziness

# CBD: new miracle drug?

- Used for seizures, spasticity, pain, sleep, anxiety, and aggression
- Problems: inadequate data and unknown dosing of over the counter preparations
- Autism:
  1. Barchel et al. decreased rage, SIB, and hyperactivity and improved sleep in 68%, worse 5-9% Front Pharm 2019
  2. Schleider et al. Less rage, restlessness, and agitation in 80-90%, worse 10% Nature 2019



# Summary

---

- Start with complete assessment
- Behavioral treatments are essential
- Medications can help: autism and challenging behaviors-risperidone, aripiprazole, alpha adrenergics; ADHD-stimulants, atomoxetine, guanfacine; anxiety and depression-serotonin reuptake inhibitors
- Watch for adverse effects, drug interactions