AGGRESSIVE BEHAVIOR MANAGEMENT AND BEHAVIORAL CHALLENGES IN TSC

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CARING CLINIC

Presentation outline

- Overview of TAND – neuropsychiatric and behavioral challenges
- Approach to evaluation of behavioral problems
- Medications for behavioral problems

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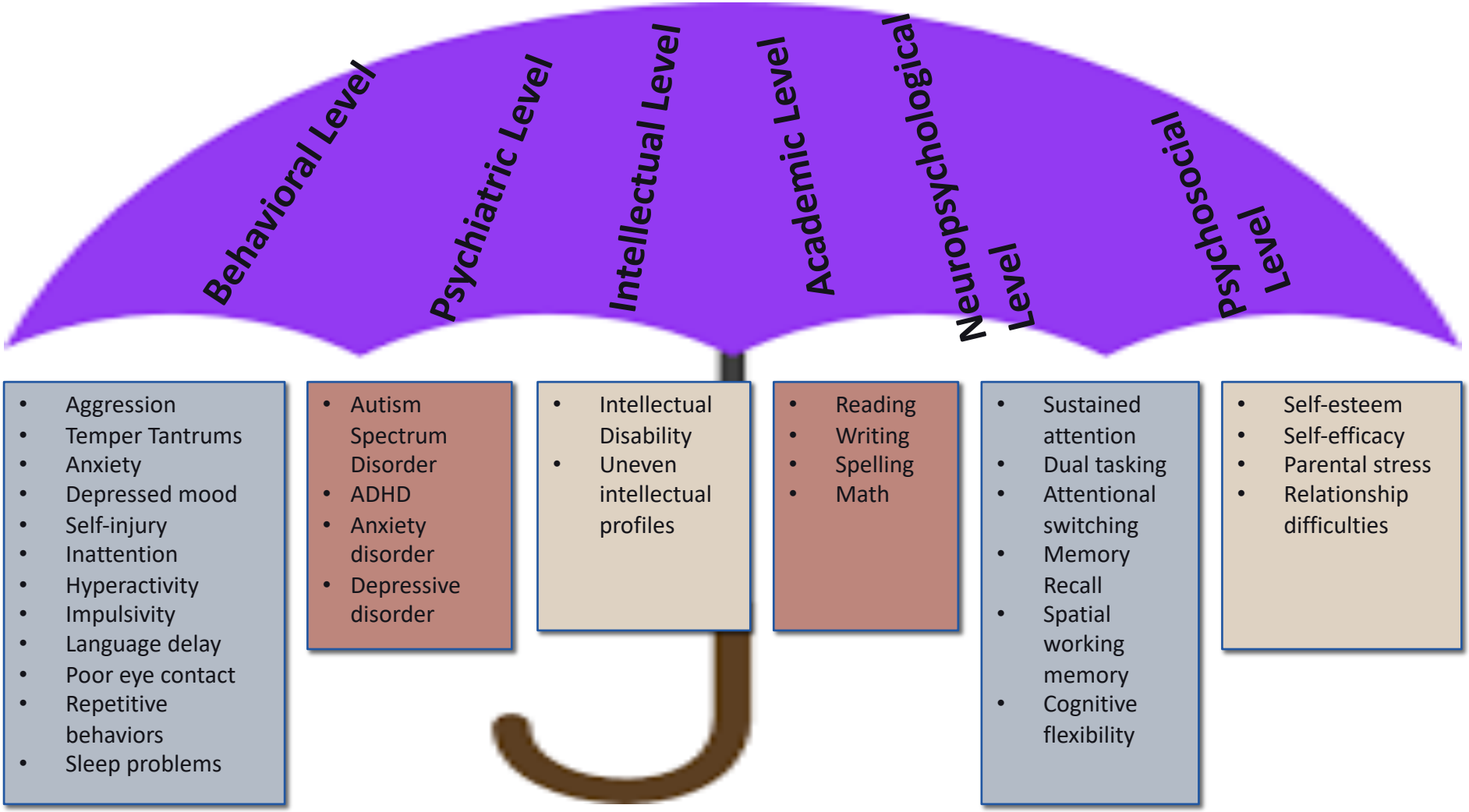
Center for Autism Research and Treatment at UCLA

TAND (TSC associated neuropsychiatric disorders)



DeVries P et. al. Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND) and the TAND Checklist. Pediatric Neurology 2015.

Tuber**O**us **SC**lerosis registry to increase disease **A**wareness (TOSCA)

- International disease registry designed to address knowledge gaps in the natural history and management of TSC
- Baseline "core" data from 2093 patients from 170 sites across 31 countries
- Ages ranged from birth to 71

Kingswood C, et al. Tuberous Sclerosis registry to increase disease Awareness (TOSCA): baseline data on 2093 patients. Orphanet Journal of Rare Diseases 2017.
De Vries P, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOCSCA natural history study. Orphanet Journal of Rare Diseases 2018.

TSC-Associated Neuropsychiatric Disorders (TAND) features reported in TOSCA at baseline

TAND features	Patients with manifestation, n/patients with available data (%)	Patients with available data, n/2093 (%)	Missing data, n/2093 (%)
Behavioral difficulties			
Overactivity	317 (20.7)	1533 (73.2)	560 (26.8)
Sleep difficulties	301 (19.5)	1540 (73.6)	553 (26.4)
Impulsivity	297 (19.4)	1533 (73.2)	560 (26.8)
Anxiety			(28.4)
Mood swings			(28.4)
Severe aggression			(25.5)
Depression mood			(28.3)
Self-injury			(25.7)
Obsession			(28.1)
Psychosis			(27.7)
Hallucination			(27.8)
Psychiatric disorders			
ASD	291 (20.7)	1406 (67.1)	687 (32.8)
ADHD	260 (19.6)	1329 (63.4)	764 (36.5)
Anxiety			(38.2)
Depression			(37.8)
Intellectual Ability[a]			
Normal			
Mild ID			
Moderate ID			
Severe ID	75 (9.1)	NA	NA
Profound ID	21 (2.6)	NA	NA
Academic difficulties			
Patients ever had difficulties in acaden performance			(43.7)
Patients assessed for academic difficul			
Neuropsychological difficulties			
Patients ever had any neuropsychologi assessed			(39.3)
Patients with performance < 5th percentile	281 (55% of those who had neuropsychological assessment)	281 (13.4)	NA

Anxiety in 9.1%
Depression in 6.1%
ADHD in 19.6%
ASD in 20.7%

822 had IQ testing and 451 (54.9%) had mild to profound intellectual disability

Most common behavioral challenges: overactivity, sleep, impulsivity, aggression, self injury

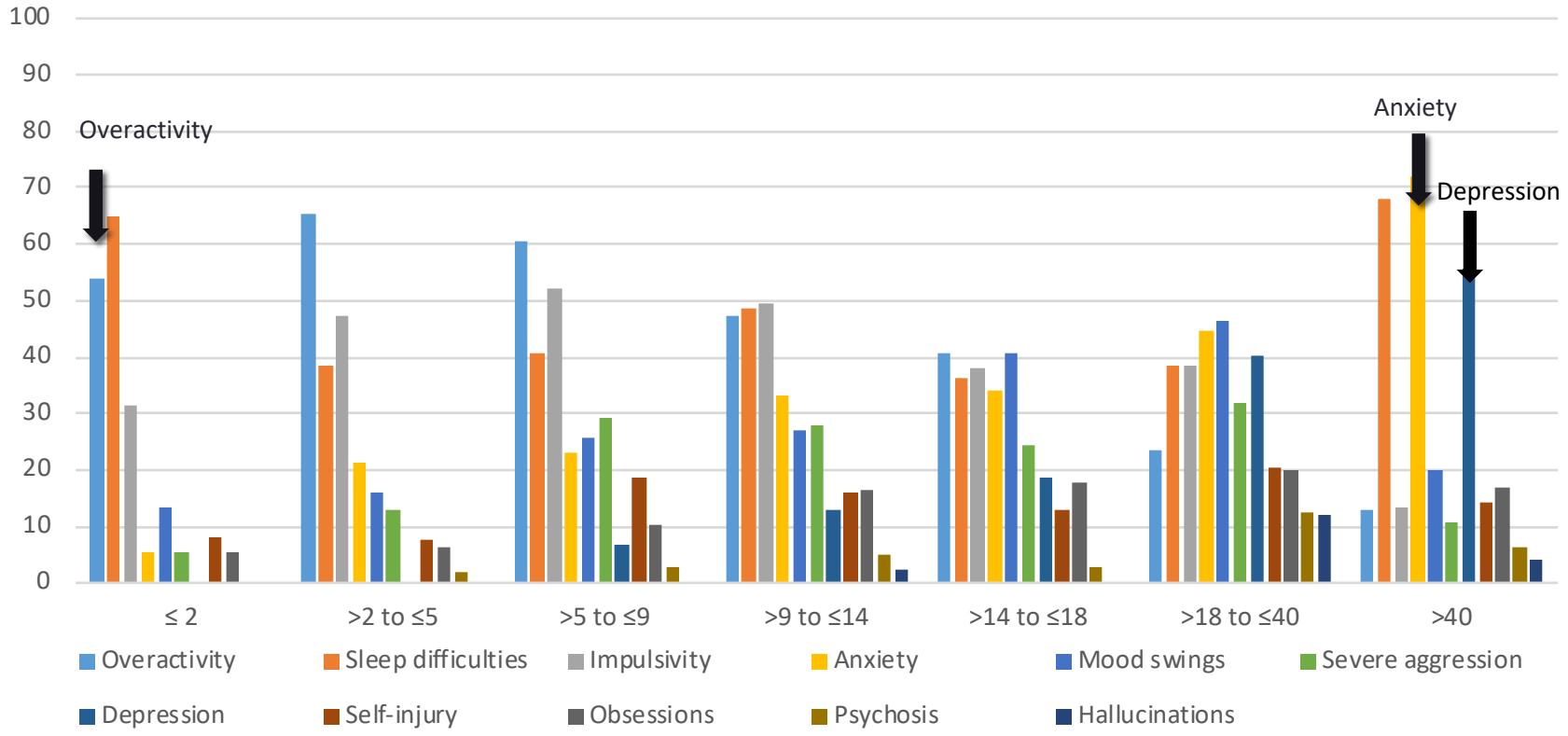
[a]Patients with intellectual ability measured by intellectual quotient were available in 822 (39.3%) out of 834 patients. Intelligent ability was not measured in 752 (35.9%) patients

De Vries P, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOCSCA natural history study. Orphanet Journal of Rare Diseases 2018.

TOSCA TAND Data

- **Anxiety**
  - diagnosed at a mean age of 17.8 years
  - affected slightly more women than men (42.4% men, 57.6% women)
- **Depression**
  - diagnosed at a mean age of 24.4 years
  - higher in women (65%) compared to men (35%)
- Higher rates of overactivity and impulsivity were observed in children
- Higher rates of anxiety, depression, mood swings, obsessions, psychosis and hallucinations were observed in adults
- **TAND was diagnosed late and not evaluated in 30-50% of patients**

TOSCA TAND Data



Anxiety and depression increased in prevalence with age

Overactivity and self-injury decreased with age

TAND and Seizures

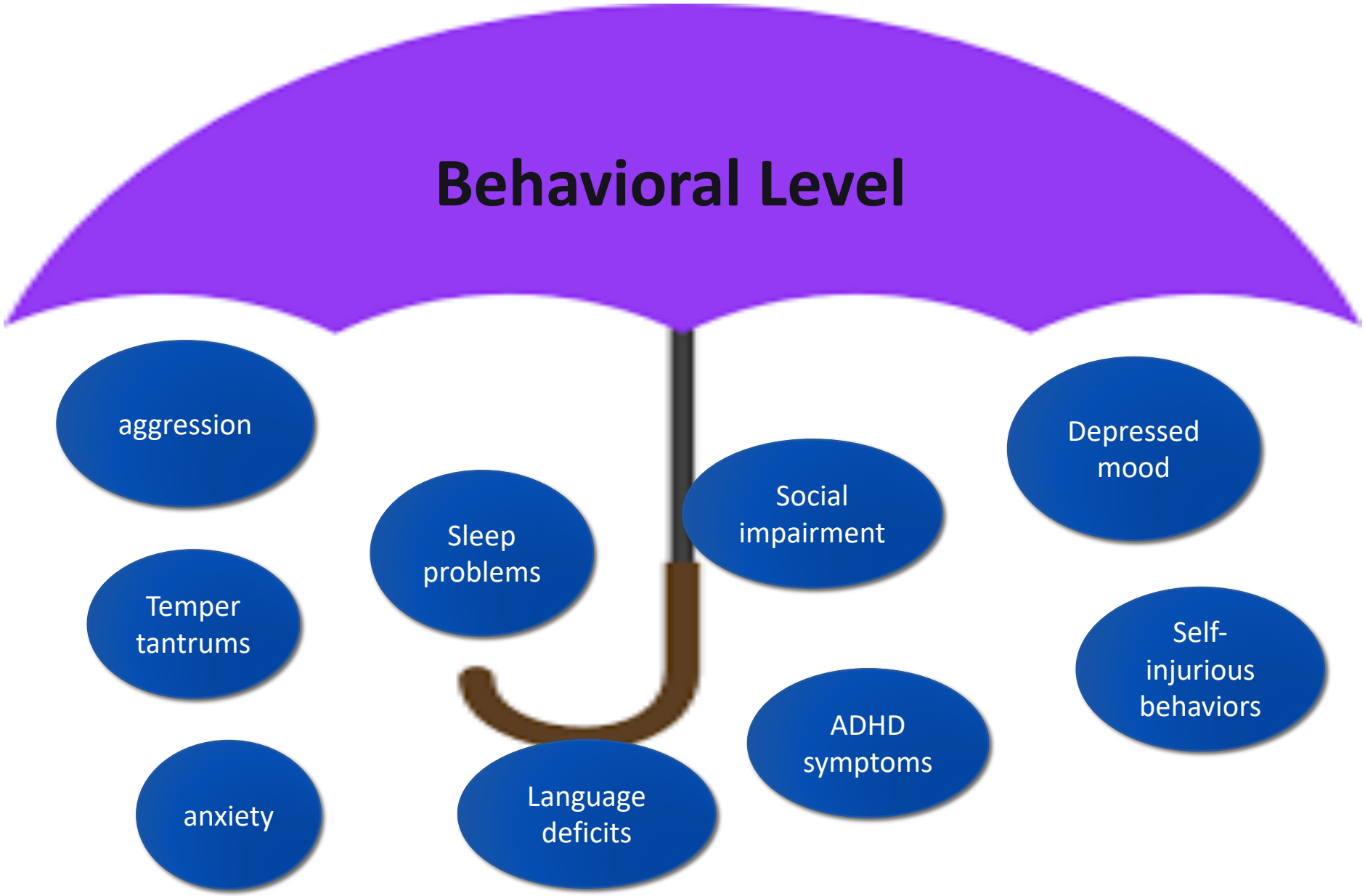
- In TOSCA, epilepsy was seen in 83.5% with over 75% presenting at 2 years or under
- Higher risk of mental health issues in individuals with epilepsy (75% in those with epilepsy vs. 37.5% in those without)[a]
- Individuals with epilepsy are more likely to have a history of ADHD and disruptive/aggressive behaviors

[a]Raznanan et al. **Psychopathology in tuberous sclerosis: an overview and findings in a population-based sample of adults with tuberous sclerosis. J Intellect Disabil Res. 2006**

90% of individuals with TSC exhibit TAND features to some extent during their lifetime

BUT

Less than 20% ever receive appropriate assessment and treatment


Behavioral Level
aggression
Temper tantrums
anxiety
Sleep problems
Language deficits
Social impairment
ADHD symptoms
Depressed mood
Self-injurious behaviors

Prevalence of TAND-related behaviors/difficulties

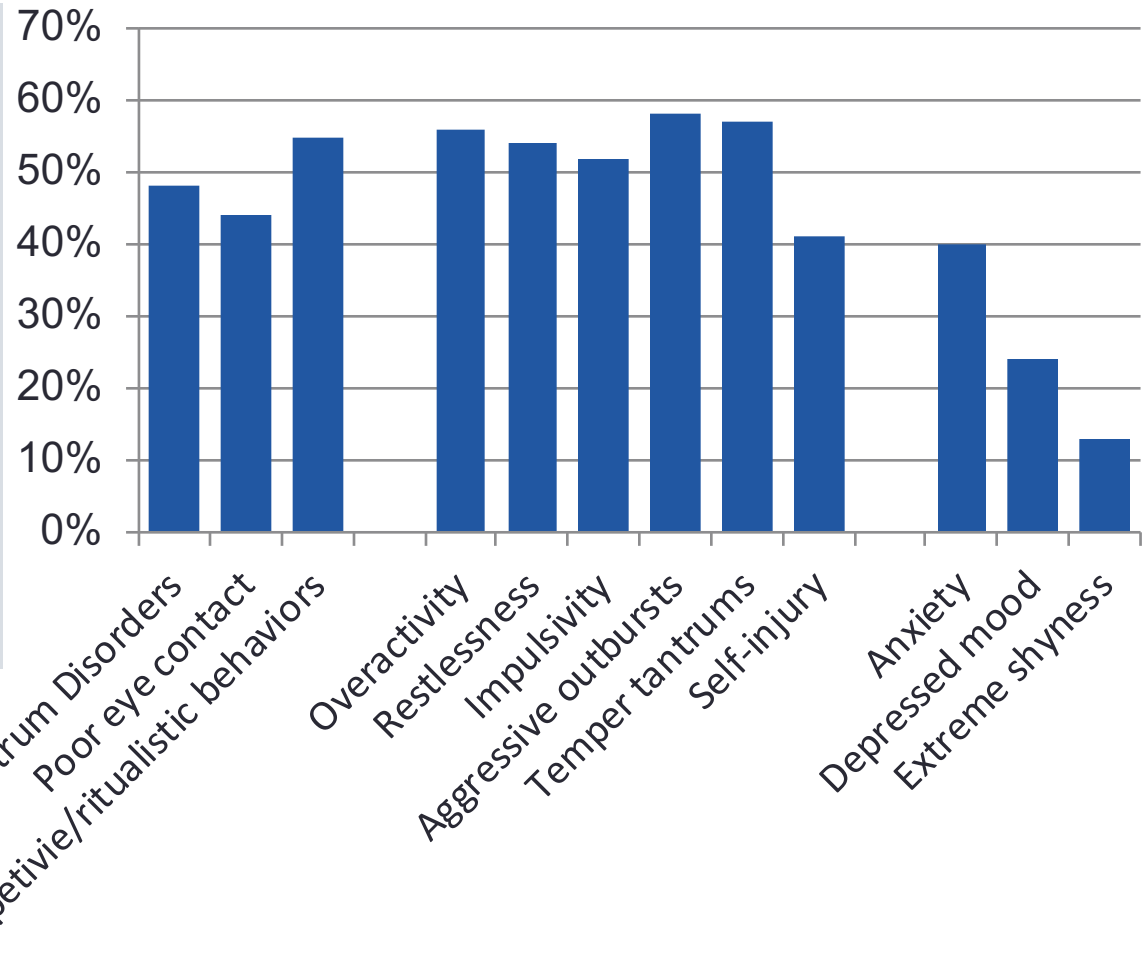
Parent questionnaire (265)

Less than 18 years

No difference in M:F

Language delays in 60%

Half considered non-verbal



de Vries et al., Eur Child Adolesc Psychiatry, 2007

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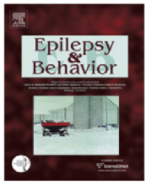

Behavior problems in children with tuberous sclerosis complex and parental stress

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- 99 pediatric patients with TSC
- Behavior problems in >40% (inattention, hyperactivity, aggression)
- Behavior problems associated with higher seizure frequency, cognitive impairment
- >50% of parents reported clinically significant parenting stress

Approach to challenging behaviors

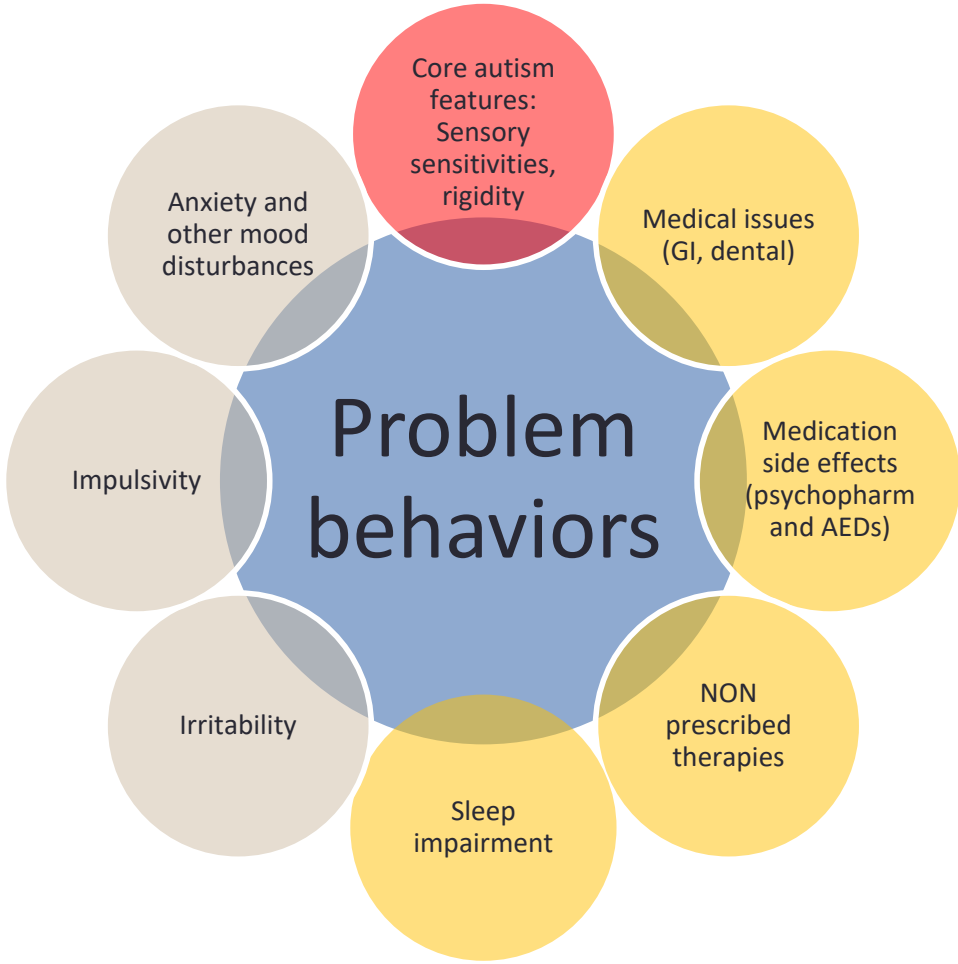
(1) TAKE A GOOD HISTORY: Ask about behaviors both at home and school, if possible gather data from teachers/aides, week-long diary, medication history

(2) Consider language and cognitive ability

(3) Try to determine underlying cause → many factors can converge onto the same aberrant behaviors

(4) Treat underlying cause through behavioral and, if needed, pharmacological approaches (rather than using medications as a Bandaid on symptoms)

(5) Often polypharmacy and med side effects are the primary problem!



Medication	Dates of use	Reason for use	Highest dose	Reason for d/c and/or SE	Benefit?
Lorazepam	2/2/2011-present	As needed for agitation	0.5 mg as needed, (some days 2-3 mg/day)	Still taking, not clear if it still helps but now needs it daily	calming
Methylphenidate LA	3/2/2012-3/15/2012	Inattention impulsivity	10 mg qam	agitation	unclear
Aripiprazole	10/1/2014-10/30/2014	Aggression	5 mg qday	Sleepiness	No
Risperidone	11/1/2014-6/2/2017	Aggression	1 mg BID	Weight gain (20 lbs)	Yes, calming
Sertraline	5/3/2015-8/10/2015	Anxiety	25 mg qday	Irritability / activation	No
Guanfacine	9/1/2017-present	Outbursts, insomnia	0.5 mg/1 mg	Constipation, some daytime sleepiness	Yes, improved sleep, calming

What are common and modifiable targets for medications?

Irritability

ADHD

Mood disturbances

Insomnia

Irritability

Two medications approved by FDA for children ages 5-16 with ASD for *irritability*

Risperidone: Partial D2 and 5HT2 receptor antagonist

Aripiprazole: Partial D2 and 5HT1A receptor agonist

Irritability comprised of 15 items from the Aberrant Behavior Checklist—not a cohesive construct

- Self-injury (3)
- Aggression (1)
- Mood (3)
- Tantrums (4)
- Loud, dysregulated behavior (4)

Courtesy of J McCracken

Drug	Staring dose	Effective Dose	Dosing	Side-effect Consideration	Monitoring Considerations
Risperidone	0.25-0.5	0.5-3	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia Sedation	Weight, BMI, Fasting glucose and lipid profile AIMS, Prolactin
Olanzapine	2.5-5	5-40	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia[1] Sedation	Weight, BMI, Fasting glucose and lipid profile, AIMS
Quetiapine	25-50	75-800	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia[1] Sedation	Weight, BMI, Fasting glucose & lipid profile, AIMS
Ziprasidone	20-40	20-160	QDAY-TID	Weight neutral?, EPS, QT prolongation Hyperprolactinemia Behavioral activation	Weight, BMI, Fasting glucose and lipid profile AIMS, ECG
Aripiprazole	2.5-5	5-15	QDAY-BID	Not quite weight neutral EPS/TD	Weight, BMI, Fasting glucose & lipids, AIMS

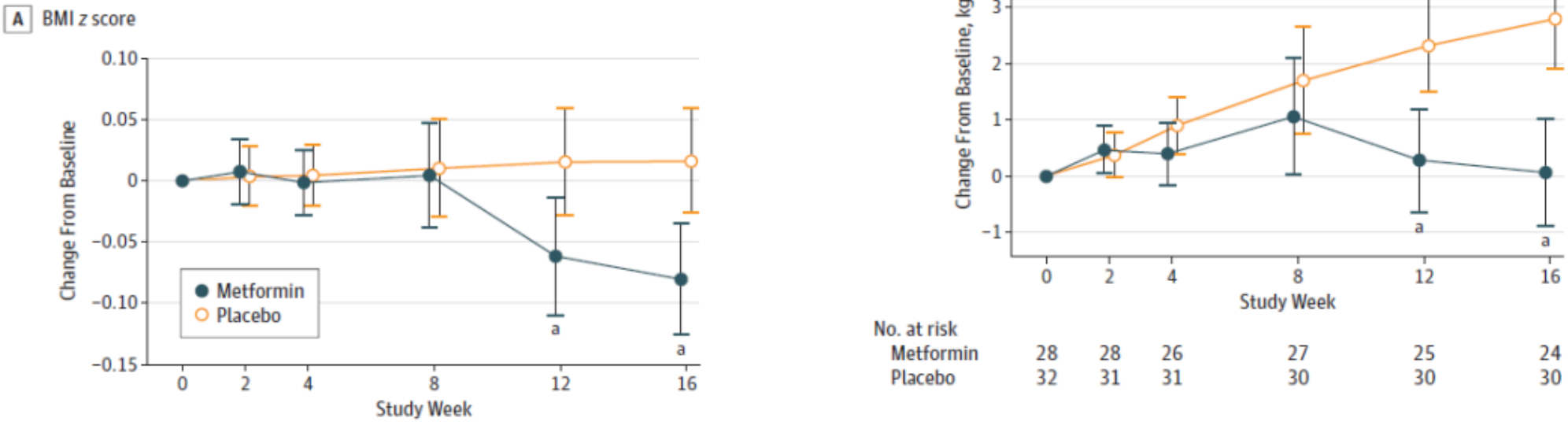
Courtesy of Dr. Anagnostou, Modified from Posey et al 2007

JAMA Psychiatry | Original Investigation

Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder
A Randomized Clinical Trial

Evdokia Anagnostou, MD; Michael G. Aman, PhD; Benjamin L. Handen, PhD; Kevin B. Sanders, MD; Amy Shui, MA; Jill A. Hollway, PhD; Jessica Brian, PhD; L. Eugene Arnold, MD; Lucia Capano, MD; Jessica A. Hellings, MD; Eric Butter, PhD; Deepali Mankad, MD; Rameshwari Tumuluru, MD; Jessica Kettel, MD; Cassandra R. Newsom, PsyD; Stasia Hadjiyannakis, MD; Naomi Peleg, MSc; Dina Odrobina, BMSc; Sarah McAuliffe-Bellin, MEd; Pearl Zakroysky, MPH; Sarah Marler, MA; Alexis Wagner, BS; Taylor Wong, BS; Eric A. Macklin, PhD; Jeremy Veenstra-VanderWeele, MD

Figure 2. Metformin Effect on Body Mass Index (BMI) *z* Score and Weight Change



Treating ADHD

- Stimulants (methylphenidate, amphetamines)
  - Target core symptoms
  - May exacerbate comorbid diagnoses (anxiety, irritability, sleep difficulties)
  - Common side effects→ decreased appetite, irritability, headaches, insomnia

- Non-stimulants (Guanfacine, clonidine, atomoxetine)
  - Alpha-2-agonists used off-label in preschool ages; also help with sleep
  - Common side effects→ drowsiness, paradoxical worsening of behaviors
  - May also help with anxiety

Treating mood disturbances

- Anxiety (SSRIs, SNRIs, Buspirone)
- Depression (SSRIs, SSNRIs, Buproprion)
- Side effects of these medications: GI (nausea), dizziness sleep issues, agitation / irritability, also can have drug interactions

Treating Insomnia

Melatonin: (RCT) 5-15 mg, given 30 minutes before bedtime, improves total sleep time by 30 minutes and significantly decreases sleep latency

Clonidine: 0.05-0.1 mg, improved sleep latency, decreased number of nighttime awakenings

Gabapentin: 5 mg/kg, one study showed improved sleep, but higher doses can cause agitation

Benzodiazepines: shorten sleep latency and increase total sleep time, but cause daytime sleepiness and risk of withdrawal

Iron supplementation: 6 mg/kg x 8 weeks, Improves restless sleep

Wright, 2011; Garstand, 2006; Wirojanan, 2009; Paavonen, 2003, Biannotti, 2006; Malow, 2011; Andersen, 2008

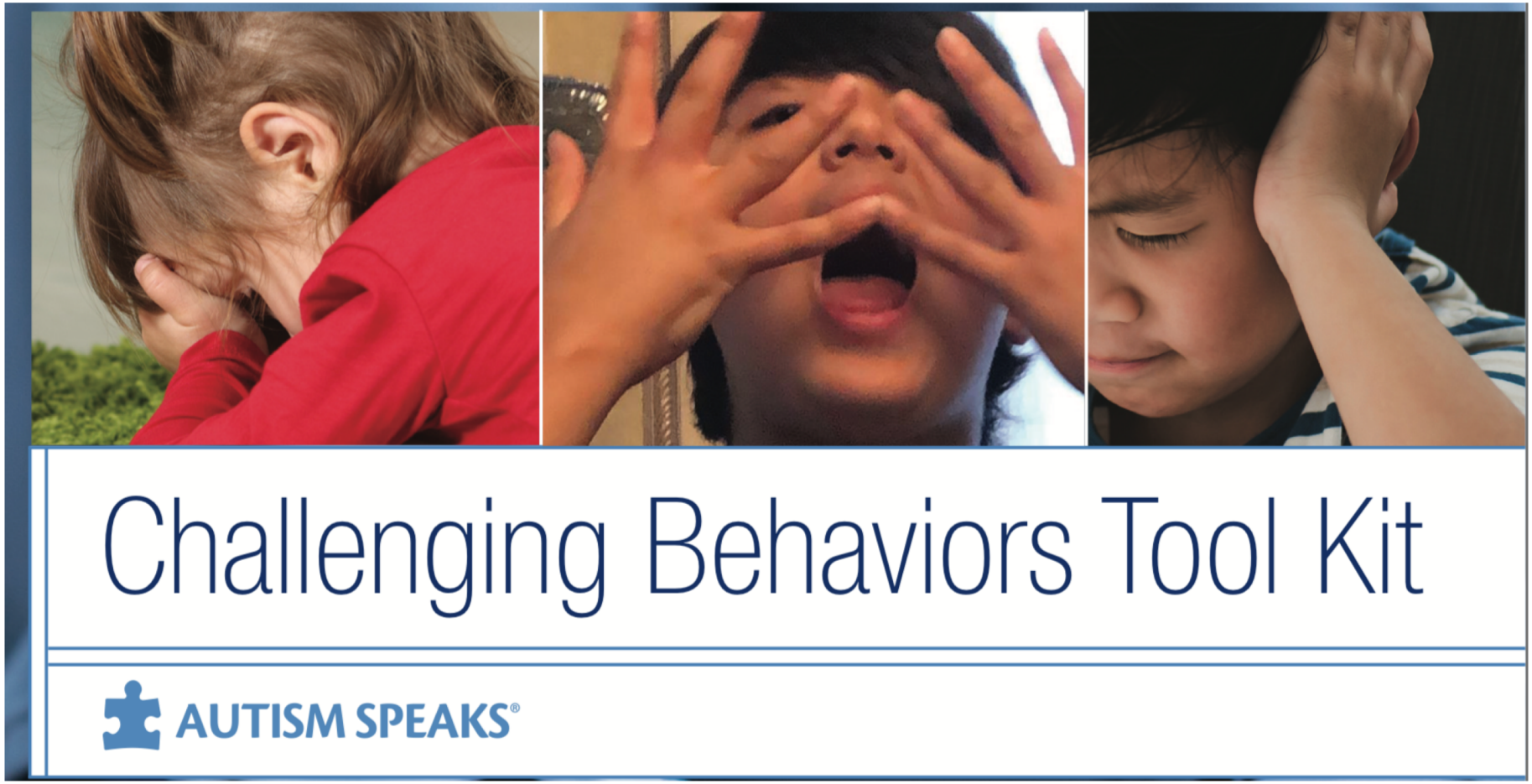
Key tips for parents

- Medications can help certain symptoms, but polypharmacy is definitely a problem and can sometimes worsen problem behaviors

- Keep track of medications (you are the best record keepers!):
  Dates of use
  Highest dose
  Reason for starting and stopping
  Adverse events / side effects
  Who prescribed it

- Always report complementary/alternative medications to your provider

- ASK WHY!



https://www.autismspeaks.org

Behavioral management strategies for challenging and disruptive behaviors...