Emotion dysregulation: coming together to treat the sickest kids…

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Disclosures

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National Institute of Mental Health		X
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Data and safety monitoring board member from the following companies: Lundbeck, Pfizer Inc.

THERE ARE NO FDA APPROVED DRUGS FOR TREATING AGITATION OR AGGRESSION IN CHILDREN SO ALL MEDICATIONS ARE OFF LABEL

Learning objectives

- Emotion dysregulation-treating the "sickest kids"
- Describe the phenomenology of outbursts
- Outline practical measurement issues
- Summarize existing treatment formulations for children with emotion dysregulation
  - Psychopharmacology
  - Psychosocial
  - Inpatient/residential
- Address the short-comings of treating actual outbursts

Jared is 7

- Referred by 2nd grade teacher for his terrible "meltdowns".
- Chronically hyperactive, impulsive, distractible and oppositional.
- Didn't want to do math, turned over his desk, sent to the principal's office and proceeded to trash that.
- Placed in a "huggy hold"; released quickly when "calm" and became destructive again.
- Rage continued until Dad picked him up from school 2 hours later.
- He does this at least weekly
- He's had outbursts since preschool.
- Diagnosed with bipolar disorder because of his "mood swings"
- Positive reinforcers for "good behavior" haven't worked.
- He goes home with outbursts because there is no place he can be put until he calms down.

How important is this problem? Frequency of referrals for outbursts

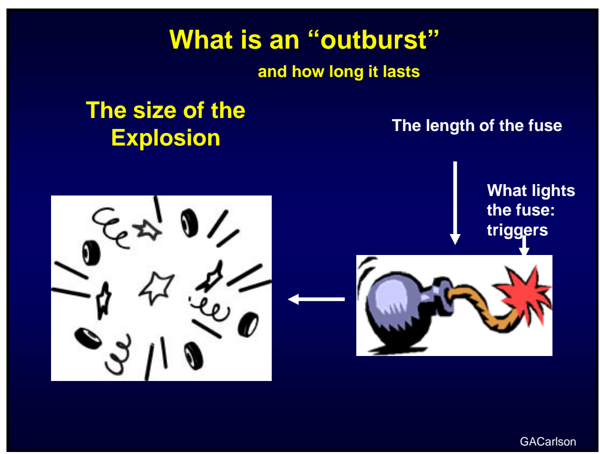
% outbursts

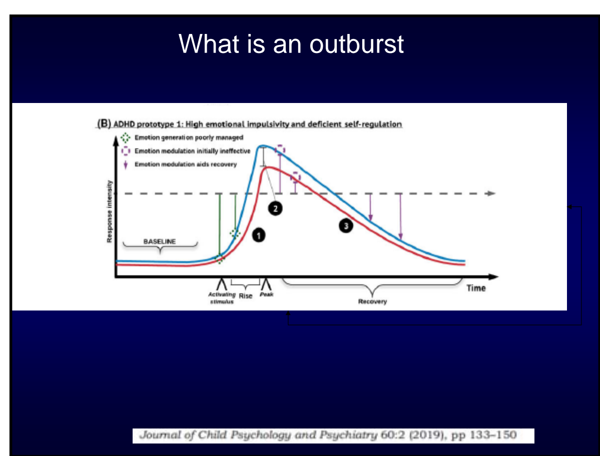
	community	outpatient	school referral	E.R.	Inpatient
N	N=457	N=2850	N=918	N=563	N=661

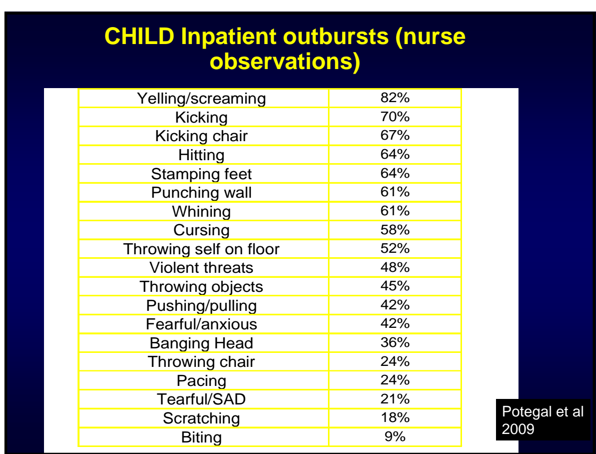
(y-axis: % , 0–80)

Does Jared have a disorder? If so, how do we define it?

- What does the child do
- Does that have any predictive significance
- How long do rage outbursts last
- Does their frequency matter
- Are outbursts ultra-rapid manic cycles or temper tantrums
- The difference between Disruptive Mood Dysregulation Disorder and Oppositional Defiant disorder is "irritability between outbursts". What does that mean?







CHILD Inpatient outbursts (nurse observations)

Behavior	%
Yelling/screaming	82%
Kicking	70%
Kicking chair	67%
Hitting	64%
Stamping feet	64%
Punching wall	61%
Whining	61%
Cursing	58%
Throwing self on floor	52%
Violent threats	48%
Throwing objects	45%
Pushing/pulling	42%
Fearful/anxious	42%
Banging Head	36%
Throwing chair	24%
Pacing	24%
Tearful/SAD	21%
Scratching	18%
Biting	9%

Potegal et al 2009

What “sickest kids” (kids whose parents are seeking help for outbursts and inpatients) do

	Outpatients with outbursts	inpatient
	125	178
Argues, whines, sulks	74.4	85.0
Swears, shouts, insults	80.8	84.5
Threatens	52.0	53.6
Slams doors, punches walls, destroys property, makes a mess	79.2	91.3
Throws things	68.8	84.5
Self-mutilates, bangs head or otherwise take it out on self	24.8	50.0
Hits, kicks, bites, spits	49.6	77.8
Needs Physical restraint	28.8	47.8

Spring and Carlson, CAClinics, in press

What outbursts and tantrums share

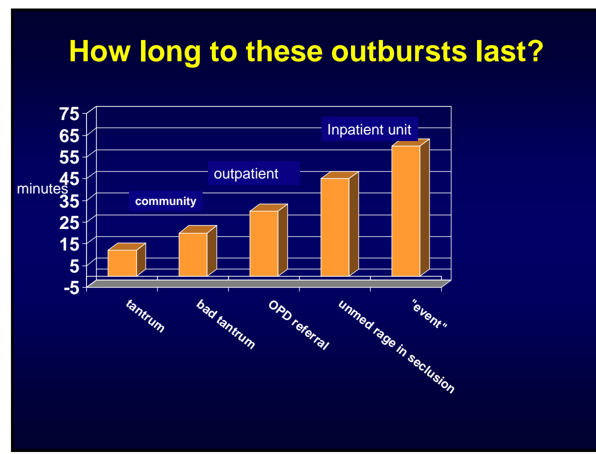
Outburst behaviors	Inpatient outbursts	Toddler Tantrums
AGITATED, ANGRY		
Scream; shout Hit; kick	X X	X X
Threaten; curse	X	
Push, pull, Throw Bite, scratch	X X	X
Pace; run away; Stamp; punch wall, bang head	X X	X
DISTRESS		
Whine, cry, anxious	X	X
Withdraw; not respond	X	

Potegal et al., Curr. Psych Reports, 2009

How often do “the sickest kids” have outbursts

	Outpatients with outbursts	inpatient
n	125	178
FREQUENCY		
<1/month	17.9	1.4
2-3X/month	22.8	33.7
At least weekly	34.7	29.5
daily	16.5	42.4
Weekly-daily	**51.2**	**71.9**

Spring and Carlson, CAClinics, in press

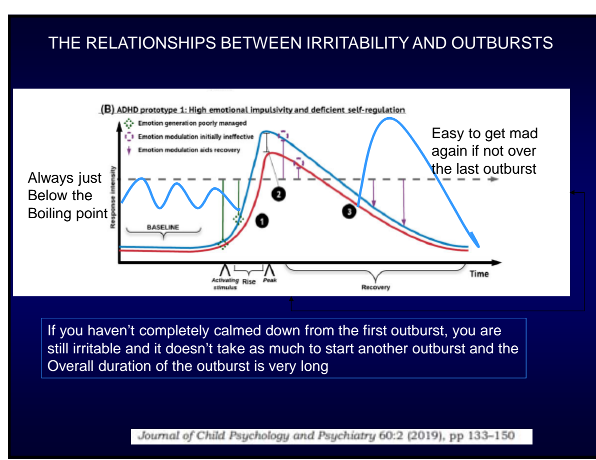


Each outburst dimension has different correlations

	Frequency (#/LOS)	Severity (IRRI)	Duration (TTC1)
age	-0.352**	ns	ns
severity	0.369**	-	0.097*
Frequency	-	0.369**	0.194**
KTEA Listen	-0.352**	-0.301**	-0.160**
KTEA Read	-0.346**	ns	ns
KTEA Math	ns	ns	-0.146**
IQ-WM	-0.231**	ns	-0.105*

* p<0.01 ** p<0.001

- **More frequent in younger kids**
- **Frequency, severity and duration are all correlated**
- **Children with problems with Listening Comprehension have more frequent and worse outbursts**



Relationship between important dimensions for kids with outbursts

WHO THE CHILD IS	Aggressive Emotionally labile
WHAT DOES THE CHILD HAVE	ADHD ODD/CD Mood disorder/DMDD Anxiety disorder PTSD Autism
HOW DOES THE CHILD FEEL	Irritable/Angry Anxious/Sad
WHAT DOES THE CHILD DO	Be crabby Be argumentative Swear, scream, cry Threaten others; threaten suicide Throw things, bang walls Destroy property Hit, kick, spit, push

WHO THE CHILD IS

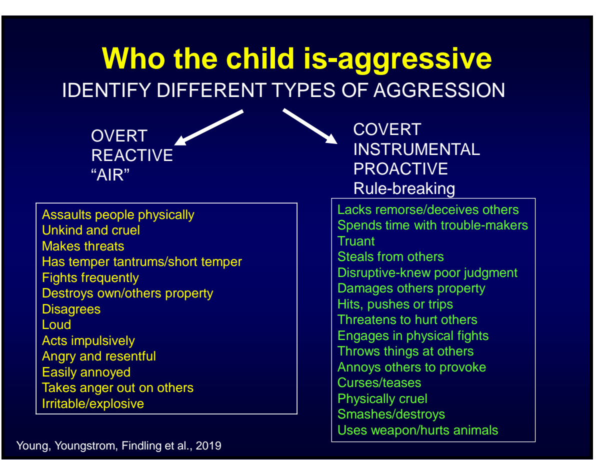
Emotion Dysregulation Inventory-Describes the child

(Mazefsky, Yu et al., 2018; 2020)

To create raw scores, sum the items for each index using the following scale: Not at all = 0, Mild = 1, Moderate = 2, Severe = 3, Very Severe = 4. Item content for each scale is included below:

	EDI Reactivity Index - Short Form (7 items)
3	Has explosive outbursts
4	Cries or stays angry for 5 minutes or longer
19	Has extreme or intense emotional reactions
21	Hard to calm him/her down when mad or upset
34	Emotions go from 0 to 100 instantly
36	Has trouble calming him/herself down
46	Reactions usually are more severe than the situations calls for

items created based on literature search, conceptual model, and clinical experience. to support item response theory (IRT) analyses, a minimum of 4 items were written for each facet and these were placed into an item Hierarchy to adequately assess of full range of emotion dysregulation



Modified Overt Aggression Scale

Verbal:

- Shouts/insults
- Severe insult/tantrum
- Threatens violence
- Threatens violence for gain

Property:

- Slams door, rips clothes, pees on floor
- Throws things, kicks furniture
- Breaks objects, smashes windows
- Sets fires, throws objects dangerously

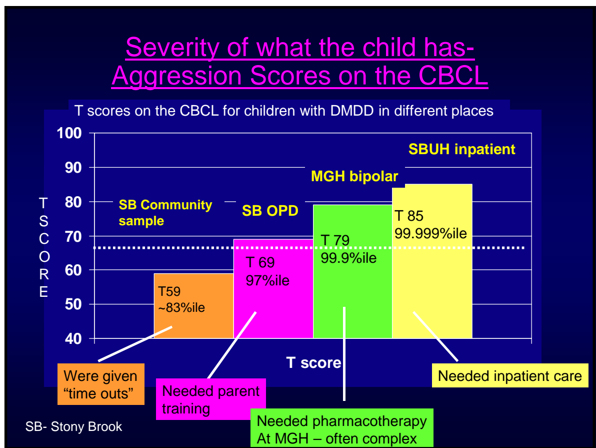
Autoaggression

- Picks at self, hits self without injury
- Bangs head, fists into walls
- Hurts self-minor cuts and bruises [self-injurious beh]
- Major injury (lost tooth) or suicide attempt

Physical aggression

- Menacing gestures
- Pushes, scratches without injury
- Attacks→mild injury
- Attacks→severe injury

Modified from Kay SR, et al (1988). Journal of Nervous and Mental Disease 176:539-546



How the child feels: Irritable. Affect Reactivity Scale (Stringaris et al., 2012)

ARI - *P*

Name of participant: Age:

For each item, please mark the box for Not True, Somewhat True or Certainly True. In the *last six months* and compared to others of the same age, how well does each of the following statements describe the behavior/feelings of your child? Please try to answer all questions.

	NOT TRUE	SOMEWHAT TRUE	CERTAINLY TRUE
Is easily annoyed by others	☐	☐	☐
Often loses his/her temper	☐	☐	☐
Stays angry for a long time	☐	☐	☐
Is angry most of the time	☐	☐	☐
Gets angry frequently	☐	☐	☐
Loses temper easily	☐	☐	☐
Overall, *irritability* causes him/her problems	☐	☐	☐

Questions about your child's anger

What the child does during an outburst: Informant completed information about triggers and behaviors

d. S/he has always been cranky and easily angered.

2. WHAT CAUSES HIM/HER TO GET ANGRY? (Please circle **ALL THAT APPLY**)

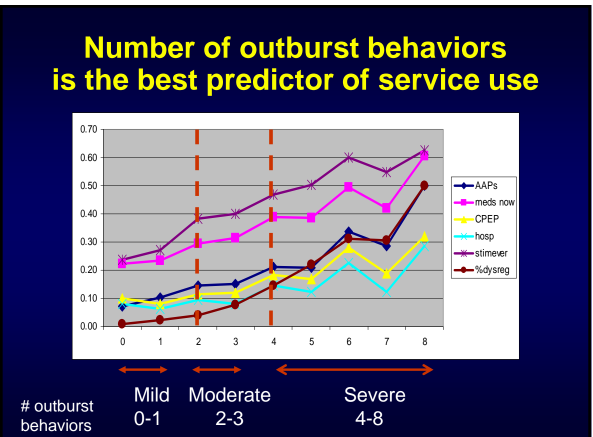
- **a.** S/he feels s/he is being criticized
- **b.** S/he misunderstands what others are saying
- **c.** Her/his demands must be met immediately
- **d.** S/he can't handle change in routine
- **e.** S/he is frustrated because s/he can't do something (task or activity)
- **f.** S/he is hungry, tired, or pre-menstrual

3. WHICH OF THE FOLLOWING DOES YOUR CHILD USUALLY DO? (Please circle **ALL THAT APPLY**)

- **a.** Expresses anger in an appropriate way (e.g., explains her/his perspective; goes to her/his room to cool down)
- **b.** Argues, whines or sulks
- **c.** Becomes verbally insulting, swears, shouts
- **d.** Threatens
- **e.** Slams doors, punches walls, makes a mess, destroys property
- **f.** Self-mutilates, bangs head, or otherwise takes it out on self
- **g.** Throws things
- **h.** Hits, kicks, bites, spits
- **i.** Needs physical restraint

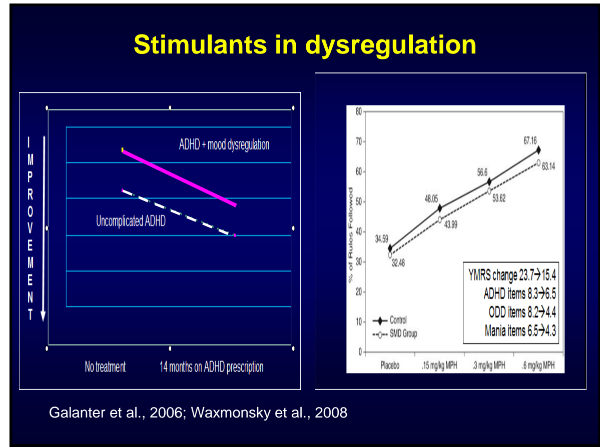
(please circle THE BEST RESPONSE to EACH QUESTION BELOW)

4. HOW OFTEN DOES A SERIOUS TANTRUM OR OUTBURST OCCUR?	a. Never___ b. Rarely___ c. several times a month___ d. Weekly_____ e. at least 3 times/week___ f. Daily___
5. HOW LONG DOES A TANTRUM OR OUTBURST LAST?	a. a few minutes ___ b. up to 15 minutes___ c. up to half an hour____ d. Up to an hour_____ e. Up to half a day____
6. IS YOUR CHILD ANGRY OR IRRITABLE BETWEEN OUTBURSTS?	a. Not at all____ b. Sometimes ____ c. often____ d. very often____
7. HOW DOES YOUR CHILD UNDERSTAND THE OUTBURST?	a. Remorseful____ b. Forgets or denies it____ c. Blames others_____ d. Spiteful______
8. WHERE DOES YOUR CHILD HAVE OUTBURSTS	a. At home/with parents____ b. at school___ c. Both home and school___ d. home, school, public___



What interventions do we have for outpatients with dysregulation?

- It depends on primary diagnosis
  - Medication management
    - Medications for aggression [E.S.~.6-.8]
    - Optimizing ADHD treatment and adding another medication where necessary
  - Psychosocial treatment
    - parent training/behavior modification [26 meta-analyses; SMD~ .4-.6]
    - Less data for CBT, collaborative problem solving and anger management
  - School interventions (in addition to above)
    - Functional behavior analysis and behavior intervention plan



How about “mood stabilizers”?

- If the mood component is separate from ADHD, what happens if you use mood stabilizers?
- Studies broad phenotype manic children with >70% ADHD + ODD comorbidity
  - Divalproex (DVP) response alone is poor.
  - Lithium alone – didn’t beat placebo.
  - ADHD comorbid children in TEAM took stimulants, but were not optimized on the dose.
  - ADHD was a moderator in the poor response to mood stabilizers and predicted risperidone response

TEAM Study-% Improved

% Subjects with CGI-BP Improvement - Mania ≤ 2

p<0.001

p<0.001

p=0.199

68.5

35.6

24.0

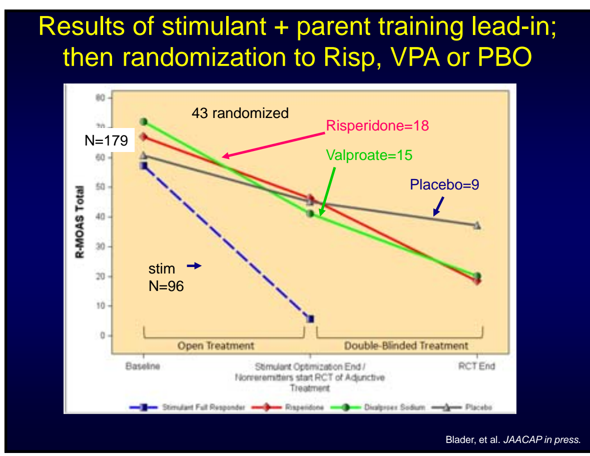
dose was 2.57±1.21mg

blood level 1.09±0.34mEq/L.

blood level 113.6±23.0

RSP (N=89) | Li (N=90) | VAL (N=100)

Geller, et al. *Arch Gen Psychiatry*. 2012;69(5):515-528.



What about antidepressants?

- UCLA trial (ages 7-17):
  - Open lisdexamfetamine (LDX) → double-blind randomization: fluoxetine + LDX (N=25) or placebo (N=25) for an additional 8 weeks.
  - **No difference between placebo and fluoxetine at 12 weeks on ADHD rating scale, CGI, Affect Regulation Inventory or Modified Overt Aggression Scale**.
- NIMH trial of MPH with citalopram (CTP)
  - Open MPH; Citalopram added double blind
  - 23 with MPH+CTP; 26 MPH+Pbo
  - CGI was the only outcome measure.
  - **Non-significant trend for end of treatment measures, no improvement in functional impairment but group by time interaction significant**.

NCT01714310
James McGough, MD (PI)

Towbin et al., JAACAP, 2019

What about treatments that address both ADHD and mood

- Current approach
  - **Maximize** response of ADHD, usually to a stimulant (not just treat; maximize)
  - Add the 2nd treatment meant to address the mood (or aggression) symptoms
    - Stimulant + risperidone [1]
    - Stimulant + lithium or divalproex [2]
    - Stimulant + antidepressant [3]

1. Barterian et al., JAACAP, 2017-TOSCA summary
2 Blader, et al. *Am J Psychiatry.* 2009; JAACAP in press
3 Tobin et al., JAACAP 2019; McGough in preparation

models for mood dysregulation aka impulsive aggression

- **Behavioral model-**
  - coercive relationship: children and parents inadvertently reinforce the wrong things perpetuating the behavior
  - Parent training/Behavior modification
- **"Frustrative non-reward"-**
  - aggression when attainment of goal is blocked"
- **Aberrant threat processing-**
  - kids misperceive the size of a threat; react to what they think is there not what is there; poor perspective taking
  - Anger management/Cognitive behavioral treatment
- **Cognitive inflexibility/Poor problem solving**
  - seeing only one unhelpful way of solving a problem and doing it over and over
  - Collaborative Problem Solving

Psychosocial treatment of primary condition

Figure 2
MATCH-Style Flowchart Conceptualizing Youth Irritability Treatment in a Modular Framework

A modular approach to youth irritability-Evans et al CAP Clinics, in press

Irritability relevant modules in MATCH

Evans et al., in press

ADHD and Impaired Mood (AIM) study

Waxmonsky et al., 2016

Children with DMDD "stabilized" on ADHD Meds

- Parent component
  - Psychoeducation; behavior modification; teaching parents about triggers; address parent's mood state
- Child group
  - "best to make choices when calm"
  - Emotion recognition, problem solving, application of coping to problem solving

Community group stabilized on med; but had treatment in community

- Results – time improved many measures.
- AIM "effect sizes"
  - 0.53 for mood index; 0.51 for CDRS (mild depressive sx)
  - 0.63 for irritability (though this didn't persist)
  - 0.42 for ODD symptoms

DBT and DBT-C

Perepletchikova, personal communication

- DBT has primary targets
  - (e.g., self-harm, suicide, therapy engagement, unemployment, skills training)
  - secondary targets (e.g., unrelenting crisis vs inhibited grieving, etc.).
- DBT-C has primary targets
  - (e.g., suicidality, NSSI, parental emotion regulation, child's verbal/physical aggression, skills, etc)
  - secondary targets (helping a parent learn how to instill in a child senses of self-love, safety and belonging).

Perepletchikova F[1], JAACAP, 2017

Inpatient treatment studies focus mostly on reduced restraints

- Acute hospital (~2-3 wks LOS)
  - 3 behavior modification-some aggressive chidlren
    - 1 child unit (reduced PRNs; reduced S/R); 2 young adolescent unit (reduced S/R)
  - 2 Collaborative Problem solving
    - 2 child units; some aggressive children
- State hospital (2-9 months)
  - Staff training-6 core strategies
    - Mostly adolescent; 30-60% aggressive
- Data are very limited
  - No aggressive measures
  - Samples not necessarily aggressive
  - Not necessarily developmentally oriented
- 1 systematic review of verbal de-escalation in adult inpatient units – no evidence that it reduces aggression

Carlson et al., 2020; Chua et al, in press; Price et al, 2015

What about the actual outbursts?

- No consensus on how to intervene otherwise with episodes; outcome measures lacking
  - Behavior modification –limit setting [2]
  - Negotiation/collaborative problem solving has a little data
  - Verbal de-escalation may backfire in a sample of children who have problems with listening comprehension and working memory; data in adults is poor; data in kids is absent.
- PRN medications are widely used but there are no placebo-controlled data to demonstrate shortening of episode [1]

[1]-Baker and Carlson, EBMH, 2018
[2]-Carlson et al., JAACAP, 2020

Studies of PRNs in children

- Many consensus articles. Rare outcome /effectiveness data.
- One DBPC ... o)
  - Oral; 5
  - No drug ... r nurse CGI
  - I-M= pla
- One system
  - Compa ... episodes
  - Outcom
    - Unn ... cated epis ... current beh
- 3 record rev ... h poorly defined out
- 5 studies of ... , mostly in teens, mostly in E-Rs with mixed effect; biggest positive effect –patient went to sleep

Baker and Carlson, 2018

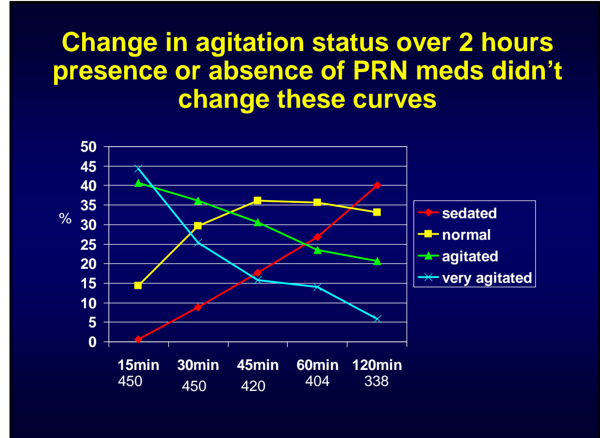
ORAL PRN meds

drug	dose	T-max; peak action
Diphenhydramine (allergy)	1.25 mg/kg elixir ~40 ± 8 mg	No sedation 1.3 ±3 hours
Lorazepam	2.5 mg 4mg	23% drowsy-40 min 67% drowsy-90 min 34% drowsy-40 min 88% drowsy-90 min
hydroxyzine		2.0±0.9 hrs; peak 5 hrs
chlorpromazine		1.5 hrs
Olanzapine -melt		6 hours
Risperidone-liq discmelt		1 hour 1.8 hours
ziprasidone		5 hours

I-M PRN meds

drug	dose	T-max; peak action
Diphenhydramine (allergy)		5-10 minutes for allergic reaction
Lorazepam	2 mg 4 mg	30% drowsy in 40 min 80% drowsy in 40 min
haloperidol		.33 to .5 hours
haloperidol + lorazepa	5 mg 2 mg	30 minutes for restrained adolescents
chlorpromazine		30 min
Olanzapine -melt		30 min
ziprasidone	20 mg	30 minutes for restrained adolescents

Change in agitation status over 2 hours presence or absence of PRN meds didn't change these curves



Things to know about outburst duration (TTC1)

	Unmedicated 1st episode*	PRN but 1st episode	TTC1 over 603 PRNs**
Mean	48 + 32 min	56 + 55 min	67 + 59 min
median	30 min	30 min	45 min

- TTC1 increases with # of outbursts/PRNs r=0.194, p=000
- TTC1 for children with 1-2 PRNs: 32±33 min; for >3 PRNs 69±59 min; p=0.002
- TTC1 shorter for distress episodes (39±29) than aggression episodes (73±60) p= 0.001
- TTC1 shorter at bedtime episodes (53 ± 44) than late afternoon episodes (74 ± 63) p=0.002
- In observed outburst episodes, there is a wide range of outburst durations within one child (from 15 minutes to 8 hours). That's important because it is hard to show any treatment impact of a PRN

No difference in TTC1 by PRN type

Risp dose equivalents =PRN+standing dose

	Frequency n	%	Risp dose equivalents	sd	Mean TTC1 Min.	SD
Diphenhydramine 25 mg,50mg	181	29.1	**3.38mg**	2.58	**65**	59
risperidone 0.5 mg, 1mg	283	45.8	**2.57mg**	2.03	**63**	57
Olanzapine 5 mg	63	10.2	**5.06mg**	2.89	**85**	63
Lorazepam, hydroxyzine	43	7.0	**3.84mg**	1.80	**65**	68
CPZ 25 mg, 50 mg	48	7.8	**3.45mg**	3.06	**68**	51
Total	618	100.0	**3.27mg**	2.52	**67**	59

P=0.118

Standing Long acting stimulants shorten the duration of the outburst in minutes

	N	Mean	SD
neither	163	**71.45**	63.533
short acting MPH or Dex	210	**79.02**	62.551
long acting amphetamine or MPH	222	**50.53**	45.352

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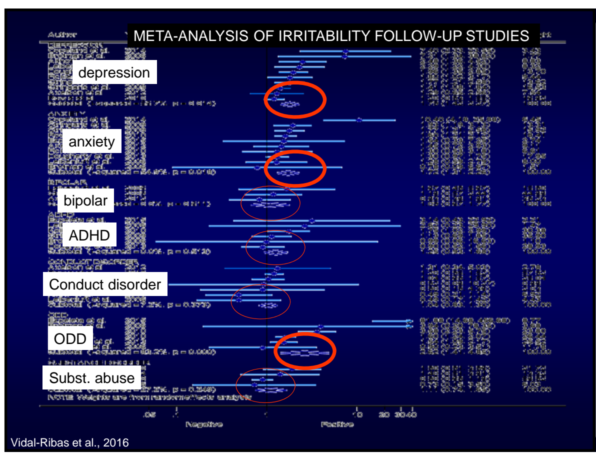
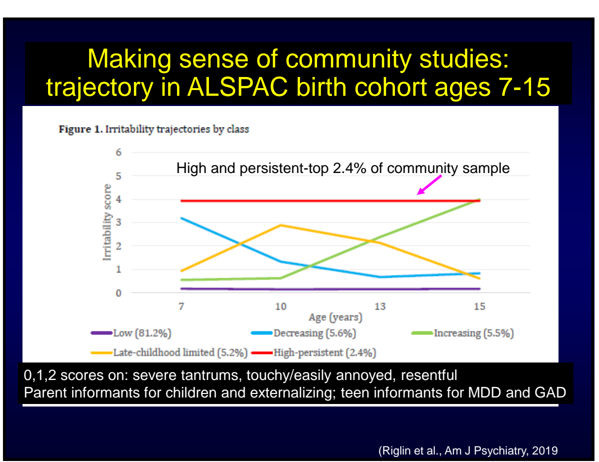
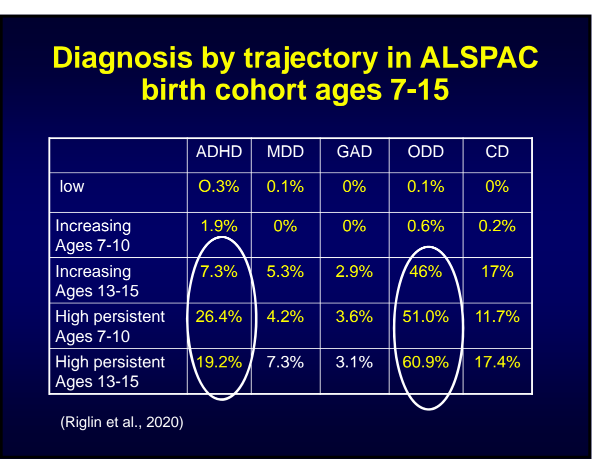
- What will happen to Jared?
- Will he outgrow his problems?
- Develop something else?







Diagnosis by trajectory in ALSPAC birth cohort ages 7-15

	ADHD	MDD	GAD	ODD	CD
low	O.3%	0.1%	0%	0.1%	0%
Increasing Ages 7-10	1.9%	0%	0%	0.6%	0.2%
Increasing Ages 13-15	7.3%	5.3%	2.9%	46%	17%
High persistent Ages 7-10	26.4%	4.2%	3.6%	51.0%	11.7%
High persistent Ages 13-15	19.2%	7.3%	3.1%	60.9%	17.4%

(Riglin et al., 2020)

What may happen to Jared? irritability grown up

- He is UNLIKELY to develop bipolar disorder
  - Continued mood and anxiety are possible outcomes
  - 2 to 5% of children who have clinical levels of "irritability" remain very significantly impaired
- Children with severe, persistent symptoms:
  - Rates of ADHD and ODD are >>mood disorder (19% ADHD; 61% ODD; 7% depression)
  - ODD /irritability symptoms attenuate but persist; much worse than "normal" so they still behave badly as adults
  - They DON'T morph into people who have only depression and anxiety; they continue to have behavior disorders the way ADHD / ODD children do as adults.

    Disruptive disorder: OR 4.6 (1.2-17.7)

    Anxiety disorder: OR 3.1 (1.1-9.6)

Bongers et al. 2004; Reef et al., 2011
Paggliacio et al., 2015; Riglin et al., 2020; Reef et al., 2010, 2011

Copeland et al., 2014
Althoff et al., 2010
Brotman et al., 2006

Bottom line

- We haven't resolved what, if any, diagnosis best describes Jared.
- We can define his outbursts. They consist of screaming, hitting, kicking, threatening, throwing things
- They have the factor structure/symptoms of preschool tantrums; there were no manic symptoms
- Median duration is 30 to 45 minutes
- Severity depends on sample (community, outpatient or inpatient)
- The more severe and persistent, the longer it lasts into the future
- Diagnostically, most children have ADHD complicated by externalizing, internalizing and learning/language disorders
- We need better outcomes measures for treatment programs
- Oral PRNs don't do much; i-ms need further study; verbal de-escalation also needs further study.