Complexities of ADHD in the Context of Autism Spectrum Disorder

ROBYN P. THOM, MD
ASSISTANT PROFESSOR, HARVARD MEDICAL SCHOOL
MARY ARMSTRONG AMORY ENDOWED SCHOLAR IN AUTISM
MGH WILLIAMS SYNDROME PROGRAM, CO-DIRECTOR

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children™

Agenda

Diagnosis

Treatment

DSM-5 Criteria for ASD

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

Social communication and interaction (3/3)

1. **Deficits in social reciprocity**
   - Abnormal social approach
   - Reduced sharing of interests or emotions
2. **Deficits in non-verbal communication**
   - Abnormal tone, body language, use of gestures
3. **Difficulty making/sustaining, understanding relationships**
   - Decreased interest in peers
   - Difficulty sharing imaginary play

+

Restricted, repetitive patterns of behavior, interests, activities (2/4)

1. **Stereotyped or repetitive** motor movements, use of objects, or speech
2. Insistence on sameness, inflexible adherence to **routines**, or ritualized patterns of behavior
3. **Highly restricted, fixated interests** that are abnormal in intensity or focus
4. **Hyper- or hypo-reactivity to sensory input** or unusual interest in sensory aspects of the environment

Social Impairment in ASD

Case examples

> *"*Sometimes I don't know when I'm being annoying and other kids don't want to play with me." – *Child with ASD*

> "Social interactions with peers have gotten more difficult to navigate over the years. And now he just wants to hang out with me and his dad. It's hard because he wants us to play basketball and surf with him." – *Mother of young adult with ASD*

> *"*I have to believe that deep down he knows I love him, but he's so in his own world that sometimes I wonder if he wouldn't notice if I died." – *Mother of adult with ASD*

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL | MassGeneral Hospital for Children

Medication Treatments

No medication has been shown to be consistently effective

Early, intensive behavioral treatments remain the gold standard of care for social impairment

Bidirectional overlap between ASD and ADHD

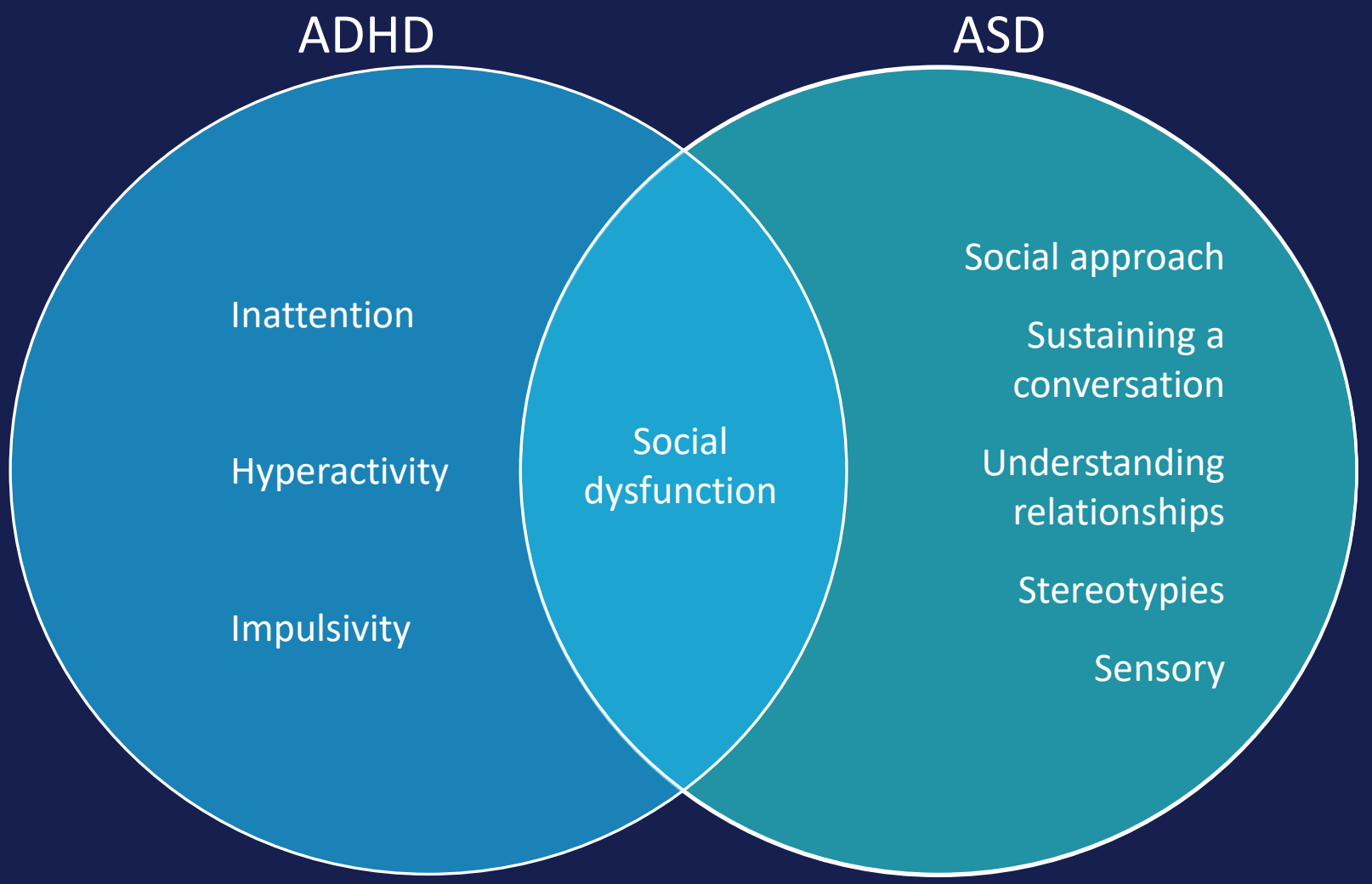
Cluster in families
Shared genetic risks
Neuroimaging findings
Male predominance

~40-70% of children with ASD have ADHD
~20% of individuals with ADHD have ASD

Systematic screening & monitoring

Co-occurrence increases the risk of another psychiatric diagnosis

Social dysfunction in ASD and ADHD



Diagnostic complexities

Engagement with special interest may mask concentration/hyperactivity problems

Resistance to change may exacerbate attentional challenges

Sensory atypicalities may affect concentration

Stereotypies may be difficult to parse from hyperactivity

Do not 'double count' symptoms.

ADHD Evaluation in a Child with ASD

Diagnostic interview + rating scales + observation + collateral

Assess intellectual ability

Assess functioning & supports across settings

Evaluate for medical, sleep, or mental health symptoms that may contribute

A comprehensive clinical evaluation is needed.

Differential Diagnosis of ADHD

Psychiatric	Medical	Environmental
Anxiety disorder	Sleep disturbance	Insufficient behavioral supports
Mood disorder	Hyperthyroidism	
Tic disorder	Akathisia	

Agenda

Diagnosis

Treatment

Nonpharmacologic Treatments

Psychoeducation: provide information about ADHD and ASD

Caregiver support & interventions

Applied Behavior Analysis to reduce problematic behaviors

Educational accommodations: breaks, reduce sensory overload, direct instructions, assistive technology, regular feedback, task prioritization, notes

Psychopharmacology for ADHD + ASD

Lower effect sizes

More sensitive to side effects, including emotionality and agitation

No studies on amphetamine salts

Most studies have focused on hyperactivity

Most research participants had intellectual disability

No studies in adults

Methylphenidate for ADHD in ASD (1/3)

4-week double-blind crossover trial of MPH -> 8-week open-label trial
5 academic sites
Dx: autistic disorder, Asperger's disorder, PDD-NOS with hyperactivity and/or impulsivity x6 months
Primary outcome measure: teacher-rated ABC-H

Test-dose phase:

72 youth (5-14 years) with ASD →

Day 1:	placebo
Days 2&3:	low-dose MPH (0.125 mg/kg TID*)
Days 4&5:	medium-dose MPH (0.25 mg/kg TID*)
Days 6&7:	high-dose MPH (0.5 mg/kg TID*)

*Third dose was a half-dose in the late afternoon

6/72 (8%) had intolerable AEs with >1 dose
16/66 (24%) had intolerable AEs at the highest dose

Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry. 2005 Nov;62(11):1266-74. doi: 10.1001/archpsyc.62.11.1266. PMID: 16275814.

Methylphenidate for ADHD in ASD (2/3)

Age, mean (SD; range), y	7.5 (2.2; 5.0-13.7)
Male, No. (%)	59 (89.4)
Race/ethnicity, No. (%)	
White	48 (72.7)
Black or African American	9 (13.6)
Asian	6 (9.1)
Hispanic or Latino	3 (4.6)
Diagnosis, No. (%)	
Autistic disorder	47 (71.2)
Asperger disorder	5 (7.6)
Pervasive developmental disorder NOS	14 (21.2)
Prior medications, No. (%)	18 (27.3)
Stimulant	6 (9.1)
α_2-adrenergic agonist	5 (7.6)
Antipsychotic	3 (4.6)
SSRI	3 (4.6)
Other	4 (6.1)
Mother's educational level, No. (%)	
High school graduate/GED or less	8 (12.1)
Some college or post–high school	25 (37.9)
College/advanced graduate or professional degree	33 (50.0)
Employed mother, No. (%)	44 (66.7)
Employed father, No. (%)	59 (89.4)
Married, n (%)	53 (80.3)
Clinical Global Impressions, severity subscale rating, No. (%)	
Moderately ill	20 (30.3)
Markedly ill	35 (52.0)
Severely ill	11 (16.7)
Slosson IQ, mean (SD; range)	62.6 (32.9; 16-135)

Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry. 2005 Nov;62(11):1266-74. doi: 10.1001/archpsyc.62.11.1266. PMID: 16275814.

Methylphenidate for ADHD in ASD (3/3)

Primary outcome measure: ABC-H teacher report

Response = CGI-I ≤2 + ≥25-30% reduction on ABC-H

Effect size: 0.2-0.54

Age, diagnosis, IQ, weight did not moderate response

49% responded to MPH (compared to 69% in MTA study)

18% exposed to MPH dropped out due to AEs (compared to 1.4% in MTA study)

Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry. 2005 Nov;62(11):1266-74. doi: 10.1001/archpsyc.62.11.1266. PMID: 16275814.

Guanfacine for ADHD in ASD (1/2)

8-week, randomized, double-blind, placebo-controlled trial of guanfacine-ER

62 children (5-14 years) with ASD and ADHD symptoms randomized to guanfacine or placebo

Primary outcome measure: parent-rated ABC-H

Secondary outcome measures: CGI-I, ADHD-RS

Characteristic	Guanfacine (N=30)		Placebo (N=32)		p
	N	%	N	%	
Male	26	86.67	27	84.38	0.99
DSM-IV diagnosis					0.31
Autistic disorder	25	83.33	26	81.25	
Pervasive developmental disorder not otherwise specified	3	10.00	6	18.75	
Asperger's syndrome	2	6.67	0	0.00	
IQ[a]					
<70	19	63.33	20	62.50	
≥70	11	36.67	10	31.25	
Clinical Global Impression-Severity					0.79[b]
Moderately ill	12	40.00	12	37.50	
Markedly ill	17	56.67	17	53.13	
Severely ill	1	3.33	3	9.38	
Tanner stage					0.99
1 or 2	29	96.67	31	96.87	
3	1	3.33	1	3.13	
Race/ethnicity[c]					0.34
White	17	56.67	23	68.75	
Black	7	23.3	4	12.50	
Asian	4	13.33	1	3.13	
Pacific Islander	1	3.33	1	3.13	
Mixed	1	3.33	3	9.38	

Scahill, L., McCracken, J. T., King, B. H., et al (2015). Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. *The American journal of psychiatry*, *172*(12), 1197–1206. https://doi.org/10.1176/appi.ajp.2015.15010055

Guanfacine for ADHD in ASD (2/2)

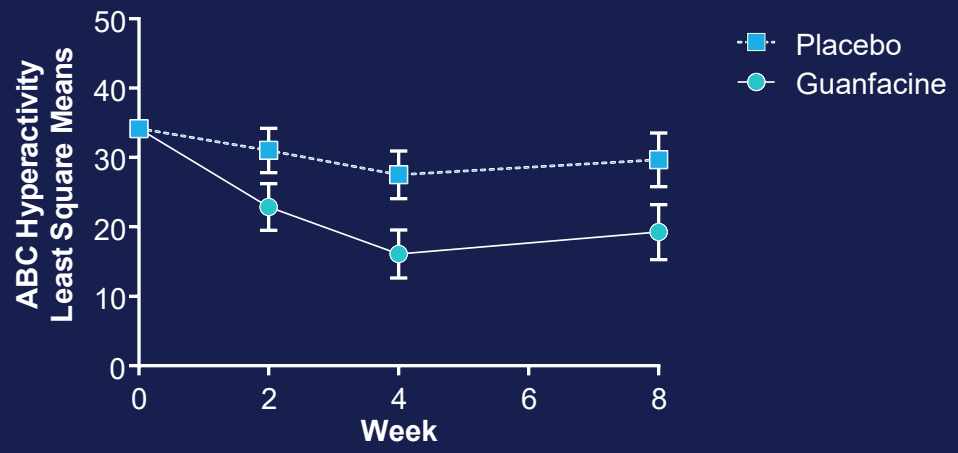
Modal dose of guanfacine-ER = 3 mg/day (range 1-4 mg/day)

43.6% decline in parent-rated ABC-H

50% guanfacine-ER vs. 9% placebo responders on CGI-I, p=0.001

4/32 (12.5%) exposed to guanfacine discontinued

Most common adverse events: drowsiness, fatigue, decreased appetite



Least squares means on Aberrant Behavior Checklist-Hyperactivity subscale scores for XR-guanfacine and placebo groups during the eight week trial. Higher scores reflect greater hyperactivity.

Scahill, L., McCracken, J. T., King, B. H., et al (2015). Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. *The American journal of psychiatry*, *172*(12), 1197–1206. https://doi.org/10.1176/appi.ajp.2015.15010055

Atomoxetine for ADHD in ASD (1/2)

STUDY DESIGN

- 8-week, double-blind, placebo-controlled trial
- 3-week titration (0.5 mg/kg/day; 0.8 mg/kg/day; 1.2 mg/kg/day)
- Primary outcome measure – investigator-rated ADHD-RS

SUBJECTS

- 97 subjects (age range: 6-17 yrs; mean 9 -10 yrs) (IQ > 60)

Characteristic	Atomoxetine n = 48	Placebo n = 49
Age, y, mean (SD), range	9.9 (2.7), 6–16	10.0 (2.9), 6–17
Male sex, n (%)	42 (87.5)	41 (83.7)
Race, n (%)		
White	48 (100)	48 (98)
African	0 (0)	1 (2.0)
Overall Wechsler IQ, mean (SD), range[a]	91.0 (16.4), 65–132	94.6 (17.7), 61–138
CGI-ADHD-S, mean (SD), range	5.0 (0.74), 3–7	5.1 (0.90), 3–7
ASD diagnosis, n (%)		
Autistic disorder[b]	26 (54.2)	32 (65.3)
Asperger's disorder[b]	3 (6.3)	2 (4.1)
PDDNOS[b]	18 (37.5)	14 (28.6)
No ASD[b]	1 (2.1)	1 (2.0)
No previous psychopharmacological treatment for ADHD, n (%)	18 (37.5)	18 (36.7)

Harfterkamp, M., van de Loo-Neus, G., Minderaa, R. B., et al. (2012). A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(7), 733–741. https://doi.org/10.1016/j.jaac.2012.04.011

Atomoxetine for ADHD in ASD (2/2)

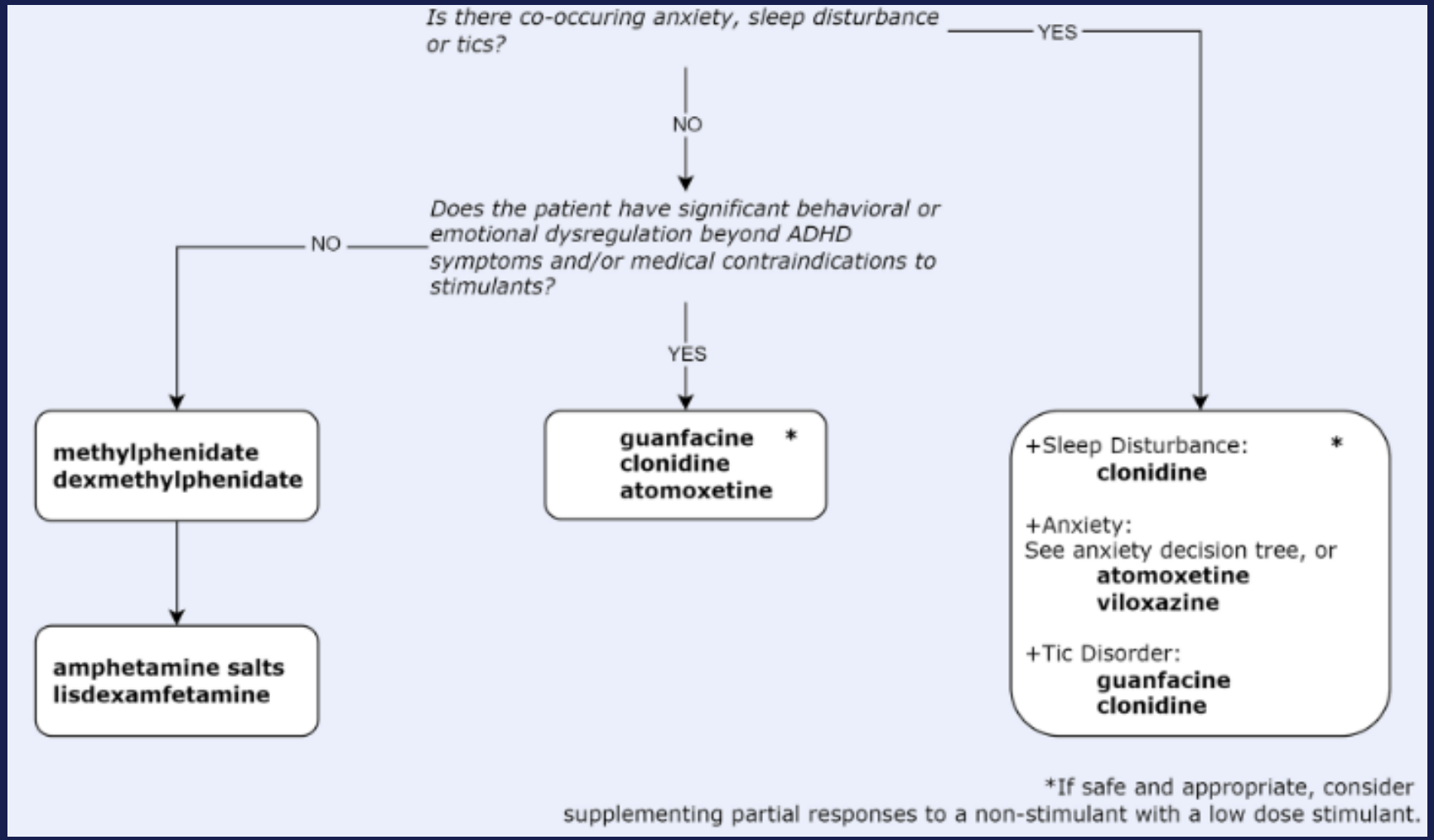
RESULTS

- ADHD-RS score change atomoxetine (-8.2) > placebo (-1.2) ($p<0.001$)
  - Greater change for hyperactivity than inattention
  - Change in ADHD-RS score is 13-19 in non-ASD children
- CGI-I: 21% atomoxetine vs. 9% placebo response rate ($p=0.14$)
- 1 discontinuation due to an AE (fatigue)

Adverse Events	ATX = 48	PLA = 49	p Value
Nausea	14	4	.009
Decreased appetite	13	3	.006
Early morning awakening	5	0	.027

Harfterkamp, M., van de Loo-Neus, G., Minderaa, R. B., et al. (2012). A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(7), 733–741. https://doi.org/10.1016/j.jaac.2012.04.011

ADHD Treatment Pathway



Manter et al. BMC Medicine. 2025. 23:11.

Thank you