Safety Matters: Trends and Learnings from the Medical Examiner



Case Review of Prescription-Related Overdose Deaths

Presenter:

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Presented to: College of Pharmacists of Manitoba

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Conflict of Interest / Disclosures

Presenter Name: Christine Leong

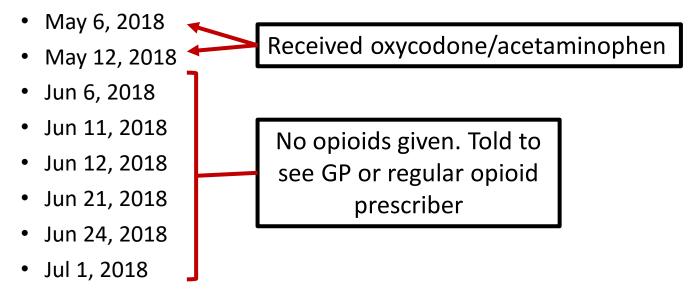
• I have no conflicts of interest to disclose

Learning Objectives

By the end of this session, you will be able to:

- Investigate dispensing patterns that contribute to the risk of overdose death
- 2. Examine the risk versus benefit of specific psychoactive medications, including combination of medications
- 3. Develop strategies for risk identification and safer dispensing practices for patients who may be at risk of overdose

- 63 year-old male with past medical history of chronic pain (following a fall from his bike with left rib fracture in May 2018), hypertension, depression
- Multiple visits to emergency department requesting oxycodone/acetaminophen due to ongoing left rib pain interfering with sleep. Already receiving acetaminophen/codeine for chronic pain



- Found unresponsive on the ground in the front yard of his home on May 6, 2019
- Transported to HSC where we was pronounced dead
- <u>Cause of death</u>: Mixed drug toxicity (cocaine, codeine, amitriptyline, gabapentin)
- Other significant conditions contributing to death: Atheromatous coronary artery disease
- Manner of death: Accidental



Toxicology

Toxicology	Level	Normal/Therapeutic
Benzoylecgonine	827 mg/dL	
Amitriptyline	250 ng/mL	
Nortriptyline	63 ng/mL	
(TCA) Total	313 ng/mL	75-200
Codeine (free)	110 ng/mL	10-100
Morphine (free)	8.9 ng/mL	10-80
Alprazolam	41 ng/mL	25-55
Gabapentin	42 ug/mL	2-20
Ethanol	23 ng/mL	0

Date Dispensed	Drug Name	Strength	Days Supply	Quantity	Prescriber
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Acetaminophen/ codeine	300/30 mg	30	120 120 60 60 120 120	Dr. X
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Alprazolam	0.5 mg 1 mg 1 mg 1 mg 1 mg 1 mg	30	120 60 30 30 60 60	Dr. X
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Amitriptyline	25 mg	30	30	Dr. Y
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Gabapentin	400 mg	30	180	Dr. Y
Apr 20, 2019	Fluticasone/salmeterol	250/25 mcg	30	120	Dr. Y
Apr 20, 2019	Salbutamol	100 mcg	25	200	Dr. Y
Apr 20, 2019 Mar 21, 2019	Zopiclone	5 mg 5 mg	30	30	Dr. Z

Date Dispensed	Drug Name	Strength	Days Supply	Quantity	Prescriber
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Acetaminophen/ codeine	300/30 mg	30	120 120 60 60 120 120	Dr. X
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Alprazolam	0.5 mg 1 mg 1 mg 1 mg 1 mg 1 mg	30	120 60 30 30 60 60	Dr. X
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Amitriptyline	25 mg	30 ombination seda	30 ting medications	Dr. Y
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Gabapentin	400 mg	30		Dr. Y rescribers for different re medications
Apr 20, 2019	Fluticasone/salmeterol	250/25 mcg	30	120	Dr. Y
Apr 20, 2019	Salbutamol	100 mcg	25	200	Dr. Y
Apr 20, 2019 Mar 21, 2019	Zopiclone	5 mg 5 mg	30	30	Dr. Z

Exposure to Concurrent Opioid-Sedating Medication Increases the Risk of Opioid-Related Deaths

RESEARCH ARTICLE

Gabapentin, opioids, and the risk of opioidrelated death: A population-based nested case–control study

Tara Gomes 1,2,3,4 , David N. Juurlink 2,3,5,6 , Tony Antoniou 1,2,7 , Muhammad M. Mamdani 1,2,3,4,6,8 , J. Michael Paterson 2,3,9 , Wim van den Brink 10

aOR 1.49 (95% CI 1.18 to 1.88)

Annals of Internal Medicine

Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study

aOR 1.68 (95% CI 1.19 to 2.36)

Research

Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study

BMJ 2015; 350 doi: https://doi-org.uml.idm.oclc.org/10.1136/bmj.h2698 (Published 10 June 2015) Cite this as: *BMJ* 2015;350:h2698

aOR 3.86 (95% CI 3.49 to 4.26)

OR 3.31 (95% CI 2.25 to 4.87)

Muscle Relaxant

OR 2.40 (95% CI 1.44 to 4.03)

Higher Daily Doses of Sedating Medications Associated with Opioid Overdose Events

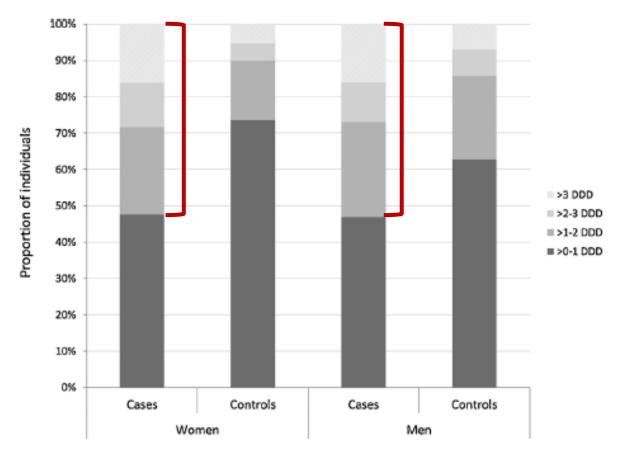
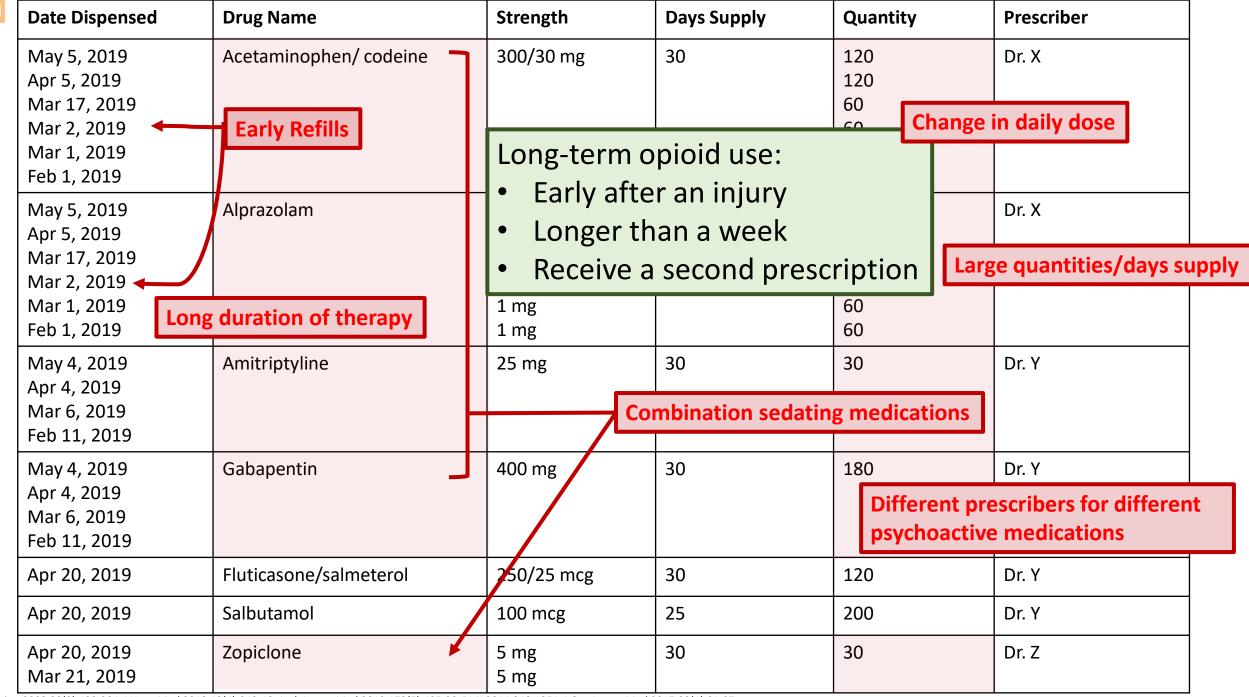


Fig. 2. Defined daily doses (DDDs) of sedating medications active on the overdose/index date, other than opioids or benzodiazepines/z-drugs.

Date Dispensed	Drug Name	Strength	Days Supply	Quantity	Prescriber
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019	Acetaminophen/ codeine Early Refills	300/30 mg	30	120	Dr. X in daily dose
Feb 1, 2019 May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Alprazolam	0.5 mg 1 mg 1 mg 1 mg 1 mg 1 mg	30	120 60 30 30 60 60	Dr. X
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Amitriptyline	25 mg	30 mbination sedatin	30 g medications	Dr. Y
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Gabapentin	400 mg	30		Dr. Y escribers for different e medications
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Apr 20, 2019	Salbutamol	100 mcg	25	200	Dr. Y
Apr 20, 2019 Mar 21, 2019	Zopiclone	5 mg 5 mg	30	30	Dr. Z

Date Dispensed	Drug Name		Strength	Days Supply	Quantity	Prescriber	
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019 May 5, 2019 Apr 5, 2019	Acetaminophen/ codeing Early Refills Alprazolam	RuLoM	unning out ea ost/stolen me Iultiple self-sa	•	se increases		
Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019			ouble-doctor se of multiple	ing e pharmacies			
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Amitriptyline	• Re	equests for sp	ther psychoac pecific medica erence for sh o	tion by bran e	d name	
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Gabapentin	• Co	oncurrent use		stances (e.g.	, alcohol, canna	abis)
Apr 20, 2019	Fluticasone/salmeterol	• 0	pposition to r	medication an	d substance	use monitoring	5
Apr 20, 2019	Salbutamol	(u	rine toxicolo	gy, unschedul	ed pill counts	s)	
Apr 20, 2019 Mar 21, 2019	Zopiclone	Ref: Jam	es J. Dealing with drug-sed	eking behavior. Aust Prescr	2016;June 39(3):96-100.		J

Date Dispensed	Drug Name	Strength	Days Supply	Quantity	Prescriber
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019	Acetaminophen/ codeine Early Refills	300/30 mg	30	120 120 60 60 Cha	Dr. X
Mar 1, 2019 Feb 1, 2019	Ri	sk of Abstine	nce / Fast tap	ering of Op	pioids
May 5, 2019 Apr 5, 2019 Mar 17, 2019 Mar 2, 2019 Mar 1, 2019 Feb 1, 2019	Alprazolam • • •	Patients lose Withdrawal s May turn to c Watch high-r	symptoms ma other sources	for opioid	ssing
May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019 May 4, 2019 Apr 4, 2019 Mar 6, 2019 Feb 11, 2019	Amitriptyline Gabapentin Ref	Recent reDuring orWhile foll	lease from income post-discharge owing supervalued atment for open	carceration ge from hos rised withdr pioid use dis	spital stay rawal or abstinence-
Apr 20, 2019	Fluticasone/salmeterol	250/25 mcg	30	120	Dr. Y
Apr 20, 2019	Salbutamol	100 mcg	25	200	Dr. Y
Apr 20, 2019 Mar 21, 2019	Zopiclone	5 mg 5 mg	30	30	Dr. Z



- Re-assess the efficacy and safety of medications to determine need for continued use
 - Drug/Medical Interactions (1. amitriptyline and cocaine/coronary artery disease, 2. Opioid coprescribed with sedating medications)
- Help create a gradual taper schedule with frequent follow-up to reduce the risk combination sedating medications
- Raise awareness on risk of physical tolerance with daily use of opioids/BZRAs and loss of tolerance after a period of abstinence/dose reduction
- Limit dispense quantities (e.g., blister packs, weekly or daily dispensing)
- Ensure **safe storage** of medication (e.g., *locked box*)



- 42 year-old male with a history of bipolar disorder, high cholesterol, obesity (BMI 43), hypertension, and migraines
- Died in his sleep on couch while watching TV in living room at home Aug 23, 2019
- <u>Cause of death</u>: Mixed drug toxicity (morphine, hydromorphone, cetirizine, cyclobenzaprine, gabapentin, hydroxyzine, mirtazapine, clonazepam)
- Other Significant Conditions: Renal failure
- Manner of death: Accidental



Toxicology	Level	Normal
Morphine	310 ng/mL	10-80
Hydromorphone	3 ng/mL	1-30
7-aminoclonzaepam	18 ng/mL	20-140
Cetirizine	1400 ng/mL	
Cyclobenzaprine	100 ng/mL	3-32
Gabapentin	26 ng/mL	2-20
Hydroxyzine	39 ng/mL	30-80
Mirtazapine	37 ng/mL	28-64
Quetiapine	110 ng/mL	100-1000



Date Dispensed	Drug Name	Strength	Days Supply	Quai	ntity	Prescriber
Aug 21, 2019	Amlodipine	10 mg	7	7		Dr. X
Aug 14, 2019	Clonazepam	2 mg	7	21		
Aug 7, 2019 Jul 31, 2019	Cyclobenzaprine	10 mg	7	21		
Jul 24, 2019	Duloxetine	60 mg	7	Combina	tion sedat	ing medications
Jul 17, 2019	Gabapentin	600 mg	7	28		
Jul 10, 2019 Jul 3, 2019	Hydroxyzine	25 mg	7	21	Long dur	ation of therapy
Jun 26, 2019	Mirtazapine	30 mg	7	7		
Jun 19, 2019 Jun 12, 2019	Morphine SR	100 mg	7	14	High-dos	
Jun 5, 2019	Prazosin	2 mg	7	14	acting m	orpnine
May 29, 2019	Quetiapine	300 mg	7	14		
May 22, 2019	Ramipril	10 mg	7	7		
Aug 1, 2019	Salbutamol	100 mcg	21	200		
Jul 24, 2019	Fluticasone/vilanterol	200/25mcg	30	30		



Dose-dependent risk of overdose

- No dose-response effect for pain relief or functional recovery (moderate quality evidence)
- Dose-dependence increase in risk of nonfatal and fatal overdose:

Dose (MEQ/day)	Overdose Rate (95% CI) per 100 000 person-years	Hazard Ratio for Overdose Event (95% CI)
None	36 (13-70)	0.31 (0.12-0.80)
<20 mg	160 (100-233)	1.00
20-49 mg	260 (95-505)	1.44 (0.57-3.62)
50-99 mg	677 (249-1317)	3.73 (1.47-9.50)
100 mg	1791 (894-2995)	8.87 (3.99-19.72)

- Patients on ≥90 MEQ/day should be prioritized for gradual opioid tapering
- Renal and liver function monitoring
- Consider referral to Respirologist / Sleep Study assessment (high opioid dose, respiratory disease, increased BMI)
- Naloxone kit
- Avoid opioid and other sedating medication (e.g., BZRAs, gabapentin, muscle relaxants)
 - Involve an allied specialist (e.g., psychiatrist, addictions medicine) to review co-prescribing of opioids and other sedating medications

- Actively engage patient (better pain control and QOL)
- Optimize non-opioid/non-pharm, psychosocial support
- Set realistic functional goals
- Have a plan to manage withdrawal symptoms and emerging pain/reduced function
- Opioid rotation to facilitate dose reduction

- Unintentional overdose
- Sleep-related breathing disorder



- 39 year-old female
- Past medical history of depression, anxiety
- Mother deceased Jan 2018
- Has two teenage children with ex-husband
- Recently fired from job; criminal matter

- Found lying on bed in basement bedroom of her residence by boyfriend on Apr 26, 2018
- Empty pill bottles and open alcohol containers were on the bedside table
- Texted boyfriend at 1:30am that she was sad and lonely. Boyfriend received text later that day and contacted emergency services
- <u>Cause of death</u>: Mixed drug overdose (topiramate, bupropion, cyclobenzaprine)
- Other significant conditions: Hepatic cirrhosis
- Manner of death: Undetermined



Toxicology	Level	Normal
Clonazepam	3.7 ng/mL	20-70
7-aminoclonazepam	22 ng/mL	20-140
Bupropion	400 ng/mL	50-100
Hydroxybupropion	6100 ng/mL	
Cyclobenzaprine	88 ng/mL	3-32
Topiramate	140 ug/mL	5-20
Ethanol (urine)	82 mg/dL	0 mg/dL



Date Dispensed	Drug Name	Strength	Days Supply	Quantity	Prescriber
Mar 20, 2018	Bupropion	150 mg	30	60	Dr. X
Nov 4, 2017		150 mg		60	
Nov 15, 2016	Not regularly taken	300 mg		30	
Oct 6, 2016		300 mg		30	
Aug 27, 2016		150 mg		60	
May 15, 2018	Clonazepam	0.5 mg	30	90	Dr. X
Mar 20, 2018				90	
Feb 27, 2018				90	Lawre amountities /
Nov 4, 2017				90	Large quantities /
Oct 6, 2017				90	Long duration of use
Jul 12, 2017				60	
May 3, 2017				60	
Mar 24, 2017				60	
Nov 15, 2016				60	
Oct 6, 2016				60	
May 15, 2018	Quetiapine	25 mg	30	60	Dr. X
Mar 20, 2018	Quetiapine not prese	ent	30	60	
Feb 27, 2018	in toxicology report		60	120	
Jan 13, 2018	m compared y report		30	60	
Dec 21, 2017			30	60	

- Return unused medication
- Antidepressant counseling
- Suicide risk assessment

- 1. Physical symptoms should improve within 3 weeks
- 2. Non-physical [cognitive and emotional] symptoms take longer but should be much better within 6 weeks
- 3. If you experience new or more intense thoughts of **suicide**, contact your doctor right away
- 4. If your **mood suddenly switches** or you have too much energy, contact your doctor right away
- Although you will likely feel better after 6 weeks, it is important that you continue treatment as recommended by your doctor
- 6. Do not stop antidepressant treatment abruptly
- Unfortunately, all antidepressants do not work for all people, so make sure to follow-up with your doctor in 3-4 weeks

Appetite Sleep Psychomotor Energy

Anhedonia
Anxiety
Guilt
Helpless
Concentration
Indecisive
Overwhelmed
Memory
Sad
Self-harm

Risk Factors

- Adverse life circumstances/precipitating events
 - E.g., death, job loss, breakup, school/social failure, sexual identity crisis, trauma, abusive relationship, occupational stress, chronic isolation
- Risk is highest in first week after hospital discharge^{1,2}
 - > 1/3 of all suicides in the first year following hospital discharge occur in first month
- Patients also at high risk of nonadherence to drug therapy soon after discharge
 - Those who continue care in the community and who maintain pharmacotherapy are at lower risk³
 - Assertive community outreach to patients who are nonadherent with medications or appointments was associated with decreased suicide rates
 - Nonadherence may be due to adverse effects, lack of symptom relief, not understanding the purpose of medications



Pharmacist's role in mental health

Roles:

- Medication management
 - Adherence, deprescribe
- Social support
- Collaboration/communication
- Education
 - SE's, proper use, storage, disposal
- Navigation/resources
 - Triage support, referral to community groups/HCPs
- Self-care
- Urgent triage

Challenges:

• Stigma

Motivational Interviewing
Trauma-informed
Community resources/contact list on hand

- Limitations within community practice (staffing, unpredictable workflow, privacy issues, time)
- Knowledge, skills, competence in area
- Communication
- Trust between pharmacist and patient
- Saying "no"
- Lack of remuneration for services

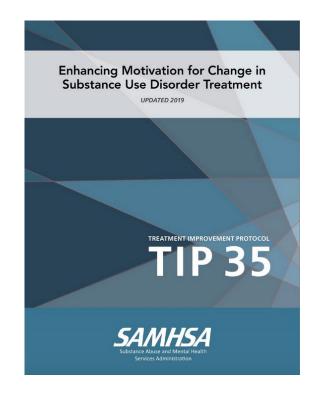
"Protecting patients. ...I've had some patients come back when they've got ...better and thank me for being on top of not giving them stuff. ...some patients are appreciative. So you're just trying to help them and protect them" – FGR3



Further Learning

- 1. BCCSU-UBC Continuing Professional Development. Addiction Care and Treatment Online Course. 15 accredited hours. Free.
- 2. SAMHSA. TIP 35: Enhancing Motivational Interviewing for Change in Substance Use Disorder Treatment. Oct 2019. Free.
- CAMH. Motivational Interviewing: Introduction and Application Course (Online). 22 accredited hours. \$650.
- 4. CAMH. Understanding Stigma. 3-6 hours non-accredited. Free





Take Home Messages

- 1. Avoid combination sedating medications where possible
- 2. Prioritize those taking >90 mg MEQ/day with close monitoring and frequent check up's on those going through a tapering schedule
- 3. Watch drug shortages, changes in strengths/dose (including tapering), new starts provide **education** and **follow-up**
- 4. Re-evaluate long duration of use and quantities provided

Questions

• E-mail: Christine.leong@umanitoba.ca

Crisis Phone List

Mobile Crisis Unit	940-1781
Crisis Stabilization Unit	940-3633
Sara Riel CSU	233-2756
Klinic Crisis Line	786-8686
Klinic Sexual Assault Line	786-8631
Seneca House	231-0217
Seneca Help Line (7-11pm only)	942-9276
Youth Mobile Crisis Team	949-4777
Osborne House Crisis Line (domestic violence)	942-3052
Kids Help Phone (24 hours)	1-800-668-6868



Resource Phone List

Manitoba Schizophrenia Society	786-1616
Mental Health Advocate (CMHA)	982-6100
Main Street Project	982-8245
Anxiety Disorders Association of Manitoba	925-0600
Health Links	788-8200
Addictions Foundation of Manitoba	944-6200
Age & Opportunity	956-6440
AIDS/STD Info Line	945-2437
Alcoholics Anonymous	942-0126
Narcotics Anonymous	981-1730
Addiction Line	855-662-6605
Union Gospel Mission-men	943-9904
Winnipeg Harvest	982-3660
Family Doctor Connection (M-F 8:30-4:30)	786-7111

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Presenters:

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